Exhibit 19

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	No. 1:19-md-2875-RBK

Amended Expert Report of Ali Afnan, Ph.D.

Date: January 11, 2023

Ali Afnan

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I. QUALIFICATIONS

1. I am the President and Founder of Step Change Pharma Inc., a position I have held since 2010. My role at Step Change Pharma involves, among other things, consultation regarding the registration of new pharmaceutical drugs, trouble-shooting processes related to the regulation of pharmaceutical drugs, compliance with Current Good Manufacturing Practices ("CGMP"), and assessments of CGMP remediation activities. My activities span from early-phase clinical trials to U.S. Food and Drug Administration ("FDA") readiness and inspection remediation.

2. I have more than 30 years of experience working in the pharmaceutical industry, with the majority of my experience having been acquired at AstraZeneca and the FDA.

3. Throughout my career, I have worked extensively on drug delivery in liquid and solid dosage forms. My work has required an in-depth knowledge of drug-delivery matrices, their design, and their manufacture. Additionally, my work has involved solving problems related to the manufacture and handling of drug products. I am experienced in understanding the physical and chemical attributes of excipients, and the interactions between excipients and pharmaceutical active ingredients. I am also well-versed in FDA regulations applicable to drug products and FDA processes for evaluating applications and related filings with respect to such products.

4. I received my B.Sc. in 1985 from the University of Wales Institute of Science and Technology. I received my M.Sc. in 1986 from the University of Manchester Institute of Science and Technology ("UMIST") and earned my Ph.D. at UMIST in 1989.

5. In September 1989, I joined ICI Plc. as a Measurement and Control Engineer. My responsibilities included the design and manufacture of novel and specific sampling of

pharmaceutical products, as well as measurements to facilitate the control of manufacturing processes of these products for consistent quality.

6. In January 1993, I joined AstraZeneca as a Senior Technologist in the International Technology Development Group, Pharmaceutical Engineering. My responsibilities included solving problems encountered during the manufacture of solid dosage forms, in particular the manufacture of tablets. I also led and managed a global multi-center project to innovate pharmaceutical manufacturing from 2001 onwards.

7. In May 2003, I was recruited by the FDA as a senior staff fellow and science policy advisor to the Director of the Office of Pharmaceutical Science ("OPS"). On joining the FDA, my role involved multi-center functioning across the Center for Drug Evaluation and Research ("CDER"), the Center for Biologics Evaluation and Research ("CBER"), the Office of Regulatory Affairs ("ORA") and the Center for Veterinary Medicine ("CVM"). While at the FDA, I was also one of the key contributors to the 2011 Process Validation guideline and the Process Analytical Technology ("PAT") guideline. These guidelines are used extensively by the pharmaceutical industry.

8. My functions as a senior staff fellow and science advisor to the director of OPS (now Office of Pharmaceutical Quality ("OPQ")) at the FDA required review of regulatory applications (including New Drug Application ("NDA"), Abbreviated New Drug Application ("ANDA") and Biologic License Application ("BLA")) and assessment of the review processes, training of staff reviewers, as well as compliance officers and investigators, participating in inspections, reviewing inspection reports and recommending action.

9. In that role, I also was engaged in collaborations with the European Medicines Agency ("EMA"), the United Kingdom Medicines and Healthcare Products Regulatory Agency ("MHRA"), Health Canada and the Japanese Ministry of Health, Labor and Welfare.

10. During my time at the FDA, I was also involved in facilitating submissions of both branded and generic drug applications based on PAT and Quality by Design (also known as "QbD"), which involved in-depth reviews of the processes and batch records used to prepare dosage forms.

11. From October 2006 to October 2010, I was an Adjunct Professor in the Graduate School of Pharmaceutical Sciences at Duquesne University. The subject matters covered by the courses I taught included the design and control of pharmaceutical manufacturing processes for solid oral dosage forms, the regulatory requirements for dossier submissions of pharmaceutical products, and the enhancement of drug product quality.

12. Over the course of my career, I have been the recipient of numerous awards, including Pharmaceutical Manufacturing Magazine's "Team of the Year" (an industry award in recognition of my work done at the FDA), and the FDA Commissioner's Special Citation for intra-center and inter-center collaboration in connection with drafting and finalizing pivotal Guidance and providing public training in a short time. I was also the recipient of the FDA and CDER Scientific Achievement Awards for "Outstanding Intercenter Scientific Collaboration." In 2012, I was awarded the prestigious International Pharmaceutical Federation's Industrial Pharmacy Section ("IPS") Medal for my contributions to the global pharmaceutical industry.

13. I am the author of more than 30 publications relating to the manufacturing of dosage forms and issues regarding regulatory topics. I am a past contributing editor to the

publication *Pharmaceutical Manufacturing*. I am currently a member of the editorial board for the publication *Contract Pharma Magazine*.

14. A copy of my curriculum vitae is attached to this report as Appendix A.

15. I am being compensated at the rate of $450 per hour for my time in this matter.

II. SCOPE OF REPORT

16. I have been asked to evaluate and respond to opinions offered by Plaintiffs' experts, including Susan Bain, DRSc,[1] Laura M. Plunkett, Ph.D., DABT,[2] Stephen S. Hecht, Ph.D.,[3] and Ron Najafi, Ph.D.,[4] regarding ZHP's compliance with FDA requirements, including CGMPs, in connection with its manufacture of the Active Pharmaceutical Ingredient ("API") for certain valsartan-containing drugs ("valsartan API").

17. My opinions in this case are based on my review of the materials listed in Appendix B, as well as my considerable experience in the field of FDA regulation. My opinions are also informed by an interview I conducted with Jucai Ge, QA Director, API Division at ZHP.

III. SUMMARY OF OPINIONS

18. Contrary to Plaintiffs' experts' assertions, ZHP complied with CGMP, including the United States Pharmacopeia ("USP") and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH") standards, in manufacturing and selling valsartan API.

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[1] S. Bain Expert Report, dated Oct. 31, 2022 ("Bain Rep.").

[2] L. Plunkett Expert Report, dated Oct. 31, 2022 ("Plunkett Rep.").

[3] S. Hecht Expert Report, dated July 6, 2021 ("2021 Hecht Rep.") & S. Hecht Expert Report, dated Oct. 31, 2022 ("2022 Hecht Rep.").

[4] R. Najafi Expert Declaration, dated Nov. 4, 2021) & R. Najafi Expert Report, dated Oct, 31, 2022 ("2022 Najafi Rep.").

19. ZHP conducted appropriate risk assessments for each of the relevant changes to the API manufacturing process (as defined below, the "TEA with quenching" and "Zinc Chloride" processes) based on the regulatory requirements in place, and what was scientifically known by industry and regulators, at the time those manufacturing changes were made. ZHP's analyses of both of these manufacturing processes were presented to the FDA, which reviewed and approved them June 9, 2015 (Valsartan) and February 8, 2016 (Hydrochlorothiazide-Valsartan) as part of the regulator's review and approval of the ANDAs for the finished dose drug products that included valsartan API.

20. The regulatory history of valsartan API and related drug products, relevant documents, and public statements by the FDA demonstrate that neither industry nor regulators were aware that NDMA or NDEA could form as a result of the manufacture of valsartan API using either the TEA with quenching or Zinc Chloride processes prior to the identification of NDMA in May 2018, which led to a voluntary recall of valsartan API. As the FDA has recognized, pharmaceutical manufacturers and regulators can only test for potential impurities that are known or suspected. As a result, CGMPs did not require ZHP to specifically test for nitrosamines in its valsartan API prior to May 2018.

21. ZHP conducted appropriate testing and manufacture of its valsartan API consistent with applicable USP standards. Applicable FDA guidance makes clear that manufacturers like ZHP are not required to identify impurities comprising less than 0.10% of the weight of the valsartan API within a given tablet, and there is no evidence that valsartan API contained nitrosamines above 0.10% while it was being sold. Moreover, FDA inspections and observations related to the manufacture of valsartan API prior to May 2018 were generally

positive, demonstrating that both ZHP and the regulator believed that ZHP manufactured and tested its API in conformance with CGMPs.

22. ZHP appropriately responded to the May 2018 discovery of nitrosamines in valsartan API, including by enacting a voluntary recall and withdrawing all valsartan API from the United States market.

23. The FDA's observations regarding ZHP's manufacturing and testing processes ***after*** nitrosamines were identified in valsartan API – which are based on knowledge not available at the time valsartan API was being manufactured and sold by ZHP – do not establish non-compliance with CGMPs.

24. Plaintiffs' experts lack support for the assertion that generic valsartan was adulterated because it was not bioequivalent to the brand-name Reference Listed Drug ("RLD"), Diovan. Whether a pharmaceutical drug or API is adulterated is a determination made by the FDA; a drug cannot be retroactively deemed adulterated for purposes of litigation. Moreover, the presence of trace impurities in a generic drug or drug component does not affect bioequivalence or render a drug adulterated. And in any event, an independent lab (whose nitrosamine testing has been reviewed and confirmed by Dr. Najafi) identified NDMA ***in Diovan***. Thus, even if bioequivalence were affected by trace impurities, Plaintiffs' experts' theories would still be illogical.

IV. OVERVIEW OF APPLICABLE REGULATORY REQUIREMENTS AND FDA SUBMISSIONS

25. The FDA is a regulatory agency responsible for ensuring that medications are safe, effective and properly manufactured and marketed.

26. The FDA regulates pharmaceutical manufacturers and manufacturers of API pursuant to the Federal Food, Drug, and Cosmetic Act ("FDCA"), the FDA's regulations implementing that statute, and official FDA Guidance.

27. One way the FDA ensures the quality of API and finished drug products is by monitoring compliance with CGMPs.[5] "The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product."[6] The CGMPs applicable to a pharmaceutical manufacturer vary based on whether it is manufacturing a drug product (i.e., a finished dose) or drug substance, (i.e., API).[7]

28. The CGMPs that apply to drug products, as opposed to drug substances, are defined in 21 C.F.R. §§ 210 and 211. Section 210.1(a) states that "[t]he regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."[8]

29. Pursuant to Section 211.100: "(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all

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5 *See* FDA, *Current Good Manufacturing Practice (CGMP) Regulations* (current as of 11/16/2022), https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations.

6 *Id.*

7 *Id.*

8 21 C.F.R. § 210.1(a).

requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance."[9]

30. As stated in § 210.3(b)(4): "Drug product means ***a finished dosage form***, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo."[10]

31. The ICH brings together regulatory authorities and pharmaceutical industry members to develop international ICH Guidelines. The ICH guidelines, ***which have been adopted as FDA guidance***, cover four areas: Quality (Q), Safety (S), Efficacy (E) and Multidisciplinary Guidelines (M).

32. 21 C.F.R. § 10.115(d)(1)-(3) defines the legal authority of the FDA (and thus ICH) Guidance as follows:[11]

> (1) . . . Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.
>
> (2) You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations.
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> (3) Although guidance documents do not legally bind the FDA, they represent the agency's current thinking. Therefore, FDA employees may

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9 21 C.F.R. § 211.100.

10 21 C.F.R. § 210.3(b)(4) (emphasis added).

11 https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-10/subpart-B/section-10.115.

> depart from guidance documents with appropriate justification and supervisory concurrence.[12]

33. ICH Q7 sets forth CGMPs for the manufacture of API.[13] ICH Q7 "is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess."[14]

34. ICH Q7 is very detailed and provides a complete structure for the quality system management of an API facility. It also states that a "formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API."[15] However, ICH Q7 does not specify how an activity needs to be performed.

35. With respect to impurities, ICH Q7 states that "[a]ppropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process."[16] It further states that "[s]pecifications and test procedures should be consistent with those included in the registration/filing."[17]

36. ICH Q7 does ***not*** prescribe specific testing protocols. Nor does it address regulatory reporting. Logically, it could not do so because it was developed by a group of

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12 21 C.F.R. § 10.115(d)(1)-(3).

13 FDA, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Guidance for Industry*, https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf.

14 ICH Q7 § 1.1, https://database.ich.org/sites/default/files/Q7%20Guideline.pdf.

15 *Id.* § 13.10, https://database.ich.org/sites/default/files/Q7%20Guideline.pdf.

16 *Id.* § 11.13.

17 *Id.* § 11.12.

international regulators and is used in countries throughout the world with different reporting structures and regulations.

37. ICH Q7 is also silent on nitrosamines or any other specific impurity, contrary to the suggestion of Plaintiffs' experts. (*See* 2022 Najafi Rep. at 3.)

38. ICH Q10, also referenced by Plaintiffs' experts, provides guidance about pharmaceutical quality management systems. Quality Management Systems ("QMS") are overarching systems that govern operations at a pharmaceutical facility. ICH Q10 "describes one comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts."[18] "ICH Q10 is not intended to create any new expectations beyond current regulatory requirements."[19] In other words, ICH Q10 does not impose any obligations beyond those already imposed by other ICH Guidance or federal regulation.

39. ICH Q3 "is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state."[20] ICH Q3A provides guidance for drug substance and ICHQ3(B) for finished products. Plaintiffs' experts opine that ICH Q3A requires investigation and assessment of all potential impurities and all potential degradation products of chemical reactions. (Bain Rep. at 30, 36; Plunkett Rep. at 30-31.) But ICH Q3A only provides guidance about impurities in new drug substances, not manufacturing changes to an existing API product.[21] That renders ICH Q3A irrelevant in this case, because valsartan API

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18 ICH Q10 § 1.1, https://database.ich.org/sites/default/files/Q10%20Guideline.pdf.

19 *Id.*§ 1.

20 ICH Q3A § 1, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf.

21 *Id.*

had already been registered and approved in multiple regulatory regions before ZHP filed its drug master files.[22] Thus, valsartan API is an old drug substance, not a new drug substance, and ICH Q3A's instruction to look for new impurities would not generally apply.

40. Regardless, ZHP did comply with ICH Q3A. The stated purpose of ICH Q3A makes clear that some impurity in API and FD is expected and allowed under regulatory requirements:

> Impurities in new drug substances are addressed from two perspectives . . . Chemistry [a]spects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures [and] [s]afety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.[23]

41. Impurities will always be present in products; some will be known and some will be unknown. ICH Q3A recognizes that there is no need for a new drug applicant to test for trace level impurities under a certain level – and no need to test for impurities not reasonably expected to be present in either drug substance or drug product:

> The applicant should summari[z]e the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.
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> Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential

[22] *See, e.g.*, FDA, *Drugs@FDA: FDA-Approved Drugs, NDA 021283*, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283.

[23] https://www.fda.gov/media/71727/download; *see also* https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf (similar).

> impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold. All impurities should be qualified as described later in this guidance.[24]

42. Both ICH Q3A and Attachment 1 to the FDA guidance on Q3A define the threshold approach used to determine when impurities should be reported (0.05% of the maximum daily dose), identified (0.10% of the maximum daily dose) and qualified (0.15% of the maximum daily dose).[25] Qualifying an impurity requires the manufacturer to acquire and evaluate data that establish the quantity of the impurity and its biological safety.[26] Attachment 3 to the ICH Q3A guidance document includes a decision tree for identification and qualification of impurities.[27] According to the decision tree, if an impurity is detected at a level lower or equal to the identification threshold, then no action is required.[28]

43. Plaintiffs' experts also reference ICH Q8(R2), ICH Q9, ICH Q11 and FDA Guidance on Quality Agreements, generally opining that ZHP failed to comply with CGMPs based on these guidance materials. (*See* Bain Rep. at 1, 5-6, 17-18, 29, 45-49, 55-56, 70-71, 73, 75; 2022 Najafi Rep. at 3; Plunkett Rep. at 23-24, 37-38.) These guidance documents do not relate to API manufacturers.

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[24] FDA Q3A § 3.1, https://www.fda.gov/media/71727/download; *see also* ICH Q3A § 1, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf (similar).

[25] ICH Q3A Attachment 1, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf; FDA Q3A Attachment 1, https://www.fda.gov/media/71733/download.

[26] ICH Q3A § 7, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf.

[27] ICH Q3A Attachment 3, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf; FDA Q3A Attachment 3, https://www.fda.gov/media/71733/download.

[28] ICH Q3A Attachment 3, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf; FDA Q3A Attachment 3, https://www.fda.gov/media/71733/download.

44. For one thing, as noted above and in FDA guidance documents relating to ICH Q8,[29] ICH Q9[30] and ICH Q11:[31]

> FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.[32]

45. Because no "specific regulatory or statutory requirements are cited" in Q8, Q9 and Q11, they do not provide requirements for industry and are therefore merely suggested or recommended.[33]

46. In addition, these guidance materials are substantively inapplicable. For example, FDA guidance regarding ICH Q8(R2) specifically states:

> This guidance is intended to provide guidance on the contents of section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use). The guidance does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guidance are important to consider during those stages as well.[34]

47. Drug Product Pharmaceutical Development, which is the subject of ICH Q8(R2), is neither covered by CGMP regulations nor regulated by the FDA. ICH Q8(R2) merely "describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a

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[29] FDA Q8(R2), https://www.fda.gov/media/71535/download.

[30] FDA Q9, https://www.fda.gov/media/71543/download.

[31] FDA Q11, https://www.fda.gov/media/80909/download.

[32] FDA Q8(R2) § 1.1, https://www.fda.gov/media/71535/download; FDA Q9 § 1, https://www.fda.gov/media/71543/download; FDA Q11 § 1, https://www.fda.gov/media/80909/download.

[33] FDA Q8(R2) § 1.1, https://www.fda.gov/media/71535/download; FDA Q9 § 1, https://www.fda.gov/media/71543/download; FDA Q11 § 1, https://www.fda.gov/media/80909/download.

[34] FDA Q8(R2) § 1.2, https://www.fda.gov/media/71535/download; *see also* ICH Q8(R2) , https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf.

regulatory submission in the ICH M4 Common Technical Document (CTD) format."[35] In other words, ICH Q8(R2) explains what information should be included in an NDA or ANDA, and how it should be formatted. It does not cover the pharmaceutical development process itself. Product manufacturers report the conclusions of product development work to the FDA through the various sections of the Common Technical Dossier ("CTD"), which is the drug product application submitted to the FDA (e.g., an ANDA in the case of generic valsartan drug products).[36] ICH Q8(R2) only recommends what information may be submitted to the FDA. In addition, Pharmaceutical Development, to which ICH Q8(R2) applies, is distinct from drug substance (of API) development.[37]

48. Similarly, ICH Q9, which provides guidance related to risk management, states:

> The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies.
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> The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle. It is not

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35 FDA Q8(R2) § 1.1, https://www.fda.gov/media/71535/download.

36 *Id.*

37 Compare *id.* § 1 ("The Q8 parent guidance describes the suggested contents for ***the 3.2.P.2 (Pharmaceutical Development)*** section of a regulatory submission") (emphasis added) *with* ICH Q11 § 1, https://www.fda.gov/files/drugs/published/Q11-Development-and-Manufacture-of-Drug-Substances.pdf ("This guidance describes approaches to developing and ***understanding the manufacturing process of the drug substance***, and also provides guidance on what information should be provided in Module 3 of the Common Technical Document (CTD) sections 3.2.S.2.2 – 3.2.S.2.6" (emphasis added).)

> intended to create any new expectations beyond the current regulatory requirements.
>
> It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.[38]

49. As the document itself makes clear, ICH Q9 "is not intended to create any new expectations beyond the current regulatory requirements."[39] Moreover, ICH Q9 expressly states that formal risk management processes are not always necessary or appropriate.[40] As a result, the guidance does not provide a basis for Plaintiffs' experts' assertions that ZHP, and finished dose valsartan drug manufacturers, violated CGMP because they did not conduct sufficiently formal risk assessments of Valsartan API and VCDs pursuant to ICH Q9. (*See* Bain Rep. at 71.)

50. ICH Q11 "describes approaches to developing and understanding the manufacturing process of the drug substance, and also provides guidance on what information should be provided in Module 3 of the Common Technical Document (CTD) sections 3.2.S.2.2 – 3.2.S.2.6 (see the ICH guidance M4Q: The CTD – Quality (ICH M4Q))."[41]

51. ICH Q11 relates to the ***development of the process*** for drug substances and specifically addresses the information that should be submitted through the CTD when the details of the drug substance process need to be provided in an application.[42] In short, Q11 is the

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[38] FDA Q9 § 1, https://www.fda.gov/media/71543/download; *see also* CH Q9 § 1, https://database.ich.org/sites/default/files/Q9%20Guideline.pdf (similar).

[39] FDA Q9 § 1, https://www.fda.gov/media/71543/download; *see also* ICH Q9 § 1, https://database.ich.org/sites/default/files/Q9%20Guideline.pdf.

[40] FDA Q9 § 1, https://www.fda.gov/media/71543/download; *see also* ICH Q9 § 1, https://database.ich.org/sites/default/files/Q9%20Guideline.pdf.

[41] FDA Q11 § 2, https://www.fda.gov/media/80909/download; *see also* ICH Q11 § 2, https://database.ich.org/sites/default/files/Q11%20Guideline.pdf (similar).

[42] ICH Q11 §§ 1, 8, https://database.ich.org/sites/default/files/Q11%20Guideline.pdf.

equivalent of Q8, but for drug substances, and has no bearing on CGMPs related to the testing or manufacture of API. Q11 is "relevant to the preparation and organization of the contents of sections 3.2.S.2.2 – 3.2.S.2.6 Module 3 of the Common Technical Document (ICH M4Q)."[43] Thus, Q11 does not cover how a drug substance manufacturer develops its manufacturing practices, but instead explains what can be submitted to the FDA in Sections 3.2.S.2.2-3.2.S.2.6 of an ANDA. Instead, as noted above, CGMPs for drug substances are defined in ICH Q7.

52. Plaintiffs' experts claim that Defendants violated CGMPs by failing to comply with FDA guidance on Quality Agreements provided in a document entitled "Contract Manufacturing Arrangements for Drugs: Quality Agreements."[44] (*See, e.g.*, Bain Rep. at 17-18, 45-49, 55-56, 70, 73, 75; Plunkett Rep. at 23-24, 37-38.) The introduction to this guidance document, similar to the ICH provisions above, states:

> In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.[45]

53. The only references to the FDCA and the CFR in the Quality Agreement guidance document are referrals to definitions stated therein.[46] Thus, this guidance document does not provide legally enforceable requirements for pharmaceutical product manufacturers. It is true that ICH Q7 states that "[t]here should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including

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43 FDA Q11 § 2, https://www.fda.gov/media/80909/download.

44 FDA, Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry, https://www.fda.gov/media/86193/download.

45 *Id.* § I.

46 *See, e.g.*, *id.* (defining CGMP by reference to the FDCA and CFR).

the quality measures, of each party."[47] But, as Bain acknowledges, ZHP did have quality agreements with the finished dose manufacturers. (*See, e.g.*, Bain Rep. at 70 (acknowledging ZHP had quality agreements in place with Prinston, Teva and Torrent).) Such quality agreements appropriately detail the responsibilities of the API and drug product manufacture, including with respect to quality measures, consistent with ICH Q7. (*See* PRINSTON00463676; PRINSTON00469838; ZHP00697574; *see, e.g.*, ZHP02471359; PRINSTON00161064; PRINSTON00372649; PRINSTON00160785; ZHP02030312; ZHP01940772; ZHP00343409; ZHP02601697; ZHP01941907; TEVA-MDL2875-00020279 (Teva 167); TEVA-MDL2875-00020213 (Teva 168); TEVA-MDL2875-00020214 (Teva 169); TEVA-MDL2875-00020212 (Teva 170).)

54. Plaintiffs' experts also claim that ZHP violated CGMP by failing to comply with ICH M7, which addresses mutagenic impurities. (*See* Bain Rep. at 40-41.) The current version of ICH M7—ICH M7(R1)—only became effective in the United States in March 2018 and the original version of ICH M7 was adopted by the FDA in May 2015.[48] Accordingly, while M7 may have some bearing if ZHP were considering changes to its manufacturing process for valsartan API today, ICH M7 was not in force when ZHP submitted the relevant Drug Master File amendments detailing the relevant process changes to the FDA (or when the FDA considered those amendments in reviewing ANDA applications for valsartan drug products as detailed below). ICH M7 itself notes that it is "not intended to be applied retrospectively (i.e., to

[47] FDA, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Guidance for Industry § 16, https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf.

[48] *See* M7(R1) at 1 & n.1, https://www.fda.gov/media/85885/download.

products marketed prior to adoption of this guidance)."[49] Because ZHP had completed all the manufacturing process changes before the institution of either ICH M7 or ICH M7(R1), this guidance is irrelevant to an evaluation of ZHP's conduct in making changes to its manufacturing processes years prior to that.

55. Manufacturers of API are required to document the processes used to manufacture API – including changes to those manufacturing processes over time. Drug Master Files[50] are "submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products."[51] Drug Master Files "[a]llow parties to reference material without disclosing drug master file contents to those parties."[52] They "[a]re not required by statute or regulation."[53] The utility of the Drug Master File is to keep the manufacturing process details confidential for other industry members while providing the FDA with the information the regulator needs to properly assess those processes.

56. Drug Master Files are listed by the FDA as "Active" or "Inactive."[54] Although Type II API Drug Master Files are assigned numbers when initially filed, they are not reviewed for "completeness" and acceptance by the FDA until referenced in a drug product application

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49 *Id.*§ IV; *see also* M7, Appendix 1 ("Retrospective application of the M7 Guidance is not intended for marketed products unless there are changes made to the synthesis. [If] no changes are made to the drug substance synthesis, the drug substance would not require reevaluation.").

50 Because the generally accepted abbreviation for drug master file, "DMF," is the same as that for dimethylamine, a chemical compound relevant to one of the API manufacturing processes at issue, I have only used DMF as a stand-in for "Drug Master File" when referring to a specific Drug Master File by number – e.g., DMF No. 020939, to avoid any possible confusion given the issues in this litigation.

51 FDA, *Drug Master Files (DMFs)* (lasted updated 10/24/2022), https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

52 *Id.*

53 *Id.*

54 FDA, *List of Drug Master Files (DMFs)* (last updated 10/18/2022), https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs.

and, if found satisfactory, the Drug Master File is listed on the FDA's website to allow manufacturers to reference it in their NDA or ANDA applications.[55] The use of a Drug Master File in an NDA or ANDA is subject to a Letter of Authorization being issued by the drug master file holder to the drug product manufacturer.[56] Drug Master Files include a list of users that have been "authorized" to reference the Drug Master File in their application for approval of a drug product. The FDA "reviews the technical contents of [Drug Master Files] in connection with the review of applications that reference them (e.g., NDAs, ANDAs, INDs, BLAs)."[57]

57. Every quarter, the FDA publishes a list of Drug Master Files that have been assessed for completeness.[58] The FDA lists 86 total Drug Master Files assigned to ZHP, 77 of which are "active."[59] All "active" Drug Master Files "have passed the completeness assessment and are available for reference by ANDAs under [Generic Drug User Fee Amendments]."[60] The fact that ZHP has 77 "active" Drug Master Files demonstrates that the company has a successful track record of operating its facilities in compliance with regulatory standards given that a Drug Master File is only listed as "active" (meaning that it can be used in an NDA or ANDA) if the

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55 FDA, *Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry*, at 3 (Oct. 2017), https://www.fda.gov/media/84217/download.

56 *Id.* at 7. Note that an NDA is an application for authorization to manufacture and market a new pharmaceutical product. An ANDA is an application for marketing of a generic drug. An IND, or Investigational New Drug Application, is used to initiate a clinical trial. A BLA is an authorization application for manufacture and marketing of a biological product.

57 FDA, *Drug Master Files (DMFs)* (last updated 10/24/22), https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

58 FDA, *List of Drug Master Files (DMFs)* (last updated 10/18/2022), https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs.

59 FDA, *List of Drug Master Files (DMFs): 3Q2022 Excel* (last updated 10/18/2022), https://www.fda.gov/media/159993/download.

60 FDA, *Types of Drug Master Files (DMFs)* (last updated 01/27/2021), https://www.fda.gov/drugs/drug-master-files-dmfs/types-drug-master-files-dmfs.

Drug Master File holder has established compliance with those standards.[61] Being able to demonstrate compliance with CGMPs on a regular basis through successful Drug Master File evaluations, and repeatedly being found to be in compliance with CGMP regulations, requires a vigorously functioning Quality Management System.

58. Drug Master Files related to API products are critical to the FDA's analysis of whether to approve an ANDA for a drug product. For example, the FDA itself noted in a letter to ZHP that the approval of Torrent's ANDA for a valsartan drug product in 2011 was "contingent upon adequate information being provided in a supporting DMF." (PRINSTON00070492 at 493.) This is consistent with my experience that the FDA reviews a Drug Master File in depth when considering whether to approve an ANDA application referencing it, and the FDA will not hesitate to reach out to an API manufacturer if it identifies any potential issues with its Drug Master File. In addition, the letter reflects that the FDA reviews the specific chemistry involved in the reaction and will ask questions if it has concerns. (*See id.* at 494 (asking ZHP to address the possibility of "forming the tertiary amine as a side product" and the "hydrolysis of the ester since the reaction is doing under basic conditions" related to its valsartan API prior to the TEA with quenching and Zinc Chloride process changes were made).)

59. When the process for manufacturing an API is changed, the Drug Master File holder is required to inform the clients of the changes to the section of the Drug Master File.[62]

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[61] *See* 21 C.F.R. § 314.50(d)(1)(ii)(b) (requiring that an NDA applicant "disclose the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility"); 21 C.F.R. § 314.94(a)(9)(i) (requiring the same information for ANDA applicants, "except that the information required under § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product").

[62] 21 C.F.R. § 314.420(c).

However, the Drug Master File holder is not required to provide the full details of the changes to the client. Because NDA and ANDA holders "must notify [the] FDA about each change in each condition established in an approved NDA [or ANDA] beyond the variations already provided for in the NDA [or ANDA],"[63] a change to the Drug Master File will generally require the NDA or ANDA holder to give the FDA notice of the change and trigger a review of the Drug Master File and any amendments.

60. The written procedures for the manufacture of a finished dose drug product, including the manufacturing process of the API, are also documented in the batch record.[64] The batch record is part of the ANDA, and executed batch records are submitted to the FDA for review and approval by the finished dose manufacturer at the time of the approval of the ANDA.[65] Any manufacturing changes post-approval need to be assessed for level of change and reported to the FDA. Minor changes can be reported through the finished dose manufacturer's Annual Report to the FDA. Depending on their complexity or risk, moderate changes may be reported through a notice of changes being effected ("CBE-0") or changes being effected in 30 days ("CBE-30").[66] Major changes would need to be submitted as a prior approval supplement ("PAS").[67] Criteria for the assessment of changes to a finished dose drug product, and determining the most appropriate reporting methodology, are defined in 21 C.F.R. § 314.70.[68]

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[63] 21 C.F.R. § 314.70(a); 21 C.F.R. § 314.97 ("The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental ANDAs and other changes to an approved ANDA.").

[64] *See* 21 C.F.R. § 211.186(a)(9); 21 C.F.R. § 211.188(b).

[65] FDA, *Good ANDA Submission Practices*, at V.E, https://www.fda.gov/media/110689/download ("For each executed batch record provided in Module 3.2.R, [of an ANDA] applicants should …").

[66] FDA, *Guidance for Industry Changes to an Approved NDA or ANDA*, § II, https://www.fda.gov/media/71846/download, at 3-4.

[67] *Id.*

[68] *See id.*§ I (suggesting that both NDA and ANDA holders must follow the guidance included in 21 C.F.R. § 314.70).

Pursuant to Section 314.70(a)(ii)(2), the drug application holder "must assess the effects of the change before distributing a drug product made with a manufacturing change" and submit a report based on that assessment. As a result, the proper mechanism for a drug application holder to report a change to manufacturing of a drug product or drug substance must be determined based on the information reasonably available to the drug application holder at the time the change is reported.

61. A PAS is required for "[c]hanges requiring supplement submission and approval prior to distribution of the product made using the change (major changes). . . . A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a ***substantial potential*** to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."[69]

62. Changes requiring a CBE-30 submission include changes with "moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product."[70] A CBE-0 submission is appropriate, for example, where the change to the manufacturing process involves "[a] change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess."[71] "[T]he holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change."[72]

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69 21 C.F.R. § 314.70(b) (emphasis added).

70 21 C.F.R. § 314.70(c).

71 FDA, *Guidance for Industry Changes to an Approved NDA or ANDA*, at VII.C.2, https://www.fda.gov/media/71846/download.

72 21 C.F.R. § 314.70(c)(2)(6).

63. Changes that may be described in an Annual Report include "[c]hanges in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."[73]

64. When determining which reporting mechanism to use, a drug application holder must rely on the information reasonably available at the time.

V. OVERVIEW OF VALSARTAN API REGULATORY HISTORY

A. Valsartan's Reference Listed Drug ("RLD")

65. On July 18, 2001, the FDA approved Novartis AG's NDA for Diovan, an anti-hypertensive drug (also known as an Angiotensin II receptor blocker or "ARB").[74,75] The initial NDA covered tablets of 80, 160 and 320 mg.[76] Since then, the FDA has approved multiple supplemental new drug applications ("sNDAs") addressing the manufacturing process for Diovan, with the first approval dated April 29, 2002, and the most recent dated July 22, 2021.[77]

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[73] 21 C.F.R. § 314.70(d)(1).

[74] *See* FDA, *Drugs@FDA: FDA-Approved Drugs: NDA 021283*, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283.

[75] Prior to the approval of NDA No. 021283 in 2001, the FDA had approved Novartis's NDA No. 020665 on December 23, 1996. That NDA covered Diovan capsules, however, and has since been discontinued. *See* FDA, *Drugs@FDA: FDA-Approved Drugs*, *NDA 020655* https://www.accessdata.fda.gov/scripts/cder /daf/index.cfm?event=overview.process&ApplNo=020665.

[76] *See* FDA, Approval Package for Application No. 21-283, at 4 (July 8, 2001), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021283_original_approval_package.PDF.

[77] FDA, *Drugs@FDA: FDA-Approved Drugs*, *NDA 021283*, https://www.accessdata.fda.gov/scripts/cder/daf/ index.cfm?event=overview.process&ApplNo=021283.

B. FDA Approval of Valsartan API

66. Diovan manufactured as per NDA No. 021283 is the Reference Listed Drug ("RLD") for all valsartan generic drugs approved by the FDA as therapeutically equivalent.[78] The FDA maintains a list of all the therapeutic equivalents for NDA No. 021283 on its website.[79]

67. On June 9, 2015, the FDA approved Prinston Pharmaceutical Inc's ANDA No. 204821 as an approved drug product that is therapeutically equivalent to Diovan.[80] The approved ANDA covers 40, 80, 160 and 320 mg tablets.[81] Per the FDA's website, the ANDA is still active, equivalent to Diovan, and allowed to be marketed in the United States.[82]

68. As part of its approval of Prinston's ANDA, the FDA's Office of Generic Drugs would have reviewed Prinston's ANDA application, and in doing so, considered the CGMP status of: (1) Prinston's facilities and processes for manufacturing the valsartan drug product at issue in the ANDA; and (2) ZHP's facilities and processes for manufacturing the valsartan API used in the valsartan drug product. As noted above, the FDA also considers the Drug Master File for the relevant API, including all amendments, when reviewing an ANDA for the finished dose product. If the FDA has concerns about the contents of the drug master file for the API, or the processes documented therein, it will contact the API manufacturer and report the deficiency. (*See, e.g.*, PRINSTON00070492.) Plaintiffs' experts do not cite, and I have not in my review of relevant materials identified, any evidence that the FDA raised any concern about the information in the Drug Master File for valsartan API in connection with its review of Prinston's

78 *Id.*

79 *Id.*

80 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204821.

81 *Id.*

82 *Id.*

ANDA in 2015, which occurred ***after*** both of the manufacturing process changes at issue in this case were made and documented in the drug master file.

69. Since approval of the ANDA in 2015, Prinston's drug products (40, 80, 160 and 320 mg Valsartan) continue to be considered therapeutically equivalent to the original drug product, namely Diovan.

70. At least one other international regulatory authority reviewed and approved ZHP's manufacturing of valsartan API subsequent to the TEA with quenching and Zinc Chloride process changes. On June 9, 2016, the European Directorate for the Quality of Medicines & HealthCare ("EDQM") issued a Certificate of Suitability to ZHP for its valsartan API, stating that "[a]fter examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph VALSARTAN no. 2423 of the European Pharmacopoeia . . . if it is supplemented by the test(s) mentioned below based on the analytical procedure(s) given in the annex." (ZHP00780942 at 946.) The tests referenced are "tests for residual solvents by gas chromatography," with the relevant solvents identified as ethyl acetate (not more than 500 ppm) and toluene (not more than 890 ppm). (*Id.* at 946; *see also id.* at 988-990.)

71. Finally, the United States Pharmacopeia ("USP"), which is "the only independent, not-for-profit, nongovernmental pharmacopeia in the world," also sets forth "quality, purity, strength and identity standards for medicines," including valsartan.[83] It does so by publishing documentary standards (also known as "monographs"), as well as "USP Reference Standards"

[83] Quality Matters, *What is the U.S. Pharmacopeia?* (Aug. 4, 2015), https://qualitymatters.usp.org/what-us-pharmacopeia.

(also known as "physical standards"), against which manufacturers test to ensure their compliance with the standards.[84] Many USP standards are enforceable by the FDA.[85]

72. In 2012, the USP standards only provided explicit tests for, and limits regarding, three specific compounds for Valsartan: USP Valsartan Related Compound A ($C_{24}H_{29}N_5O_3$) ("Impurity A"); USP Valsartan Related Compound B ($C_{23}H_{27}N_5O_3$) ("Impurity B"); and USP Valsartan Related Compound C ($C_{31}H_{35}N_5O$) ("Impurity C").[86] The USP standards set the limit for Impurity A at 1.0%, Impurity B at 0.2%, Impurity C at 0.1%, and set the limits for any other impurities and all impurities collectively at 0.1% and 0.3% respectively.[87] Manufacturers were also required to test for residual solvents following the guidance contained in USP 467, which endorsed the use of GC-FID.[88]

C. Valsartan API Manufacturing Process Changes

73. Between 2007 and 2013, ZHP made multiple changes in the manufacturing process, or route-of-synthesis ("ROS"), for its valsartan API. ZHP appropriately submitted Drug Master File amendments documenting each of these manufacturing changes that included an explanation of the manufacturing process and an analysis of its potential risks.

74. ZHP submitted the original Drug Master File for "valsartan drug substance," listed as DMF No. 020939, on September 24, 2007. (ZHP01520766.)[89] Among other things, Drug Master File No. 020939 set forth ZHP's proposed manufacturing process for valsartan API,

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84 *Id.*

85 *Id.*

86 *See* USP 35, Official Monographs (2012), at 4997-98.

87 *Id.*

88 USP 35, Chemical Tests (2012), <467> Residual Solvents, at 185, 189-92; *see also <467> Residual Solvents, Pharmacopeial Forum*, Vol. 33(3) (May–June 2007) (proposing new chapter "Residual Solvents").

89 *See also* FDA, *List of Drug Master Files (DMFs): 3Q2022 Excel*, at Row 20136 (last updated 10/18/2022), https://www.fda.gov/media/159993/download (listing 9/24/2007 as the submission date of DMF No. 20939).

comprising a five-step route of synthesis (the "Valsartan ROS"). (ZHP01661566 at 569-574.) Drug Master File No. 020939 used tributyl tin chloride ($C_{12}H_{27}ClSn$) as the catalyst for the reaction in Step 4 of the Valsartan ROS. (*Id.* at 575.) It is my understanding that the process described in Drug Master File No. 020939 is referred to as the "Tin Process" by experts in this litigation. This Drug Master File is no longer active.[90]

75. ZHP subsequently elected to move away from the Tin Process and submitted Drug Master File No. 023491 for the "valsartan USP (process II)" on January 22, 2010.[91] This Drug Master File is still "active" today.[92] Among other things, Drug Master File No. 023491 substituted triethylamine hydrochloride for tributyl tin chloride in Step 4 of the Valsartan ROS. (*See* ZHP01617328 (alerting customers of change from $C_{12}H_{27}ClSn$ to TEA•HCL in Step 4); ZHP02231327 at 338 (Section 3.2.S.2 of DMF No. 023491 showing use of TEA•HCL in Step 4).)

76. On April 16, 2012, ZHP submitted Amendment-002 to Drug Master File No. 023491 ("Amendment 002"). (*See* PRINSTON00071518-527.) Amendment-002 "add[ed] [a] quenching procedure after tetrazole [formation] reaction with sodium nitrite/HCl solution." (*Id.* at 522.) ZHP explained that, to optimize the tetrazole formation reaction in the TEA Process, it had to have a ratio of raw material to azide between 1:1.5 to 1:2. (*Id.* at 523.) However, "excess azide after [the] tetrazole [formation] reaction [would] introduce acidic azide gas with high toxicity and [raise] [Environmental Health & Safety] concerns during manufacturing." (*Id.* at 523.) To address the excess azide, ZHP proposed adding the quenching step "to guarantee

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90 *Id.* (listing the status of DMF No. 20939 as inactive).

91 *Id.*, at Row 22636 (last updated 10/18/2022), https://www.fda.gov/media/159993/download (listing 1/22/2010 as the submission date of DMF No. 23491).

92 *Id.* (listing the status of DMF No. 23491 as active).

[excess] azide [from the tetrazole formation reaction was] destroyed thoroughly and minimize the risk of residual azide carry-over into the final drug substance ([a] potential genotoxic impurity) and [the] environment." (*Id.* at 523.) Finally, ZHP noted that "the specification of Valsartan final substance is unchanged and there is no adverse change in qualitative and quantitative impurity profile." (*Id.* at 526.)

77. Prior to submitting this Drug Master File amendment, ZHP ran a number of tests to determine the effect, if any, that adding the quenching would have on the process. For example, in an internal summary of the valsartan process change, ZHP employees noted that "[a]dding sodium nitrite quenching operation can effectively remove azide ions in the reaction solution, and basically will not cause negative effects on product quality." (ZHP01838512 at 517 (certified translation at 4).)

78. Following Amendment-002, ZHP separated the TEA Process into two subcategories—"without quenching" (original "Process II" prior to Amendment-002) and "with quenching," which referred to product made with the change identified in Amendment-002. (*See* PRINSTON00071518 at 521-522 (listing changes in Amendment-002).)[93]

79. On December 10, 2013, ZHP submitted Amendment-004 to DMF No. 023491 ("Amendment-004"). (ZHP01713711 (cover letter of submission).) Amendment-004 changed Step 3 of the Valsartan ROS by adding DMF to facilitate the reaction in that step. The amendment also changed Step 4 of the Valsartan ROS by: (1) substituting ZnCl2 for triethylamine hydrochloride ("TEA•HCL") as the catalyst reagent; (2) substituting DMF for

[93] On March 1, 2013, ZHP submitted its Annual Report to the FDA as well as Amendment 003 to DMF No. 023491 ("Amendment 003"). (PRINSTON00072212, PRINSTON00072213-225; PRINSTON00000005 at 009.) The change summary in the Annual Report noted that while Amendment 003 proposed several changes to the equipment used in the manufacturing process, and a non-substantive format change to the product's label, "the manufacturing process ha[d] not changed." (PRINSTON00072212.)

toluene as the solvent of the reaction; and (3) adding MTBE to facilitate the reaction in that step. (PRINSTON00073102 at 104.) In the amendment, ZHP explained that it was changing from the TEA Process to the Zinc Chloride Process "to reduce racemization and waste for quality (impurity A)"[94] and to address an "EHS [Environment, Health & Safety] concern." (*Id.*) ZHP also noted that the substitution of $ZnCl_2$ for TEA•HCL provided satisfactory yields while lowering EHS and quality concerns. (*Id.* at 108.) ZHP further explained that testing showed that the new solvents DMF and MTBE, and reagent $ZnCl_2$ were all easily removable from the final product, and testing confirmed their absence in the final drug substance. (*Id.* at 113.) Following Amendment-004, ZHP referred to the process used to produce valsartan API as the "Zinc Chloride Process."

80. ZHP performed extensive research and testing for more than two years before submitting the Drug Master File amendment containing the Zinc Chloride Process. On June 16, 2011, ZHP issued a summary of its test production using the Zinc Chloride process that noted: "Overall, the crude isomers of the trial production batches were maintained at 1.0-2.0%, and there were no individual impurities that were difficult to remove by crystallization and purification. Therefore, the product quality also met the expected requirements." (ZHP02637572 at 573 (certified translation at 2).) Likewise, an Internal Change Request form dated November 27, 2011 stated that:

> The new process solves the problem of production stability in Valine methyl ester, condensation and pentanoyl reaction, and the new reaction system of zinc chloride and DMF for Tetrazole reaction is developed, which greatly improves the conversion rate of raw materials, improves the yield, reduces the yield, and reduces the three wastes. In addition, by optimizing the saponification conditions, the assay of isomer in valsartan crude is reduced and the quality of valsartan is improved. Through a large number of

[94] Impurity A is valsartan isomer, specifically: "(R)-N-valeryl-N-([2'-(1-H-tetrazole-5-yl)biphenyl-4-y1]-methyl)-valine." (ZHP02231567 at 575.)

> experimental results about optimizing process and combined with theoretical analysis, the synthesis route of new process and critical process parameters are initially determined by Huahai, and the preliminary analysis and evaluation of impurities in new process is completed, confirming that the quality of product risk is controllable. At the same time, the safety risks brought by process changes are also evaluated by Huahai, confirming that the new process is safe and reliable essentially. According to the above analysis, the zinc chloride process is stable and reliable, and has the conditions for further validation of production. The changes of original process are applied and the new process validation is organized.

(ZHP01843066 at 099.)

81. Finally, in Amendment-004 itself, ZHP confirmed that it had performed testing on the drug substance produced following the adoption of the Zinc Chloride/DMF process. In the Amendment, ZHP noted that it tested three consecutive batches for residual solvents and had "confirmed [the solvents'] … absence in our drug substance" and provided a table showing the results of the testing. (PRINSTON00073102 at 113.) It also provided a table with the testing results of nine different batches showing that no single unknown impurity detected exceeded .03% and that the total impurities – excluding Impurity A, a valsartan isomer that was analyzed separately – ranged from .04% to .09%. (*Id.* at 118-119 (*see* rows "Any other impurity" and "Total impurities excluding impurity A").) Thus, ZHP concluded that "[t]here [was] no adverse change in qualitative and quantitative impurity profile," and "the process change/optimization [had] not impact[ed] drug quality." (*Id.* at 113.)

82. Based on the evidence I have reviewed, ZHP complied with its obligations to provide notice regarding its manufacturing process changes to the finished dose manufactures that used ZHP's valsartan API in their products by submitting Change Notifications to them prior to the process changes. (*See, e.g.*, PRINSTON00132152, PRINSTON00132154; ZHP00417442, ZHP00417443, ZHP00417454; ZHP01617390.) For example, a Change Notification for the Zinc Chloride process provided detailed information regarding the manufacturing change,

including a disclosure that DMF would be added to the process as a solvent. (*See* ZHP00417454.) The Change Notification also specifically outlined and illustrated the ROS for each step of the Zinc Chloride process, noting how DMF will used in the process, including that both DMF and sodium azide (NaN_3) would be used in step 4 of the process. (*Id.* at 459.)

D. FDA Oversight of Valsartan API Manufacture

83. The "FDA has conducted international inspections since 1955."[95] "Field Management Directive (FMD 13A) describes the role and responsibility of [the FDA's Office of Regulatory Affairs] in international inspection activities. It includes the procedure for planning and scheduling international inspections, reporting results of inspectional findings, and classifying Establishment Inspection Reports (EIRs)."[96] "The inspection interval and depth of coverage of inspections are consistent with the periodic inspections of FDA's domestic program insofar as practical."[97] In 2015, the FDA explained that "[c]urrently, without statutory authority to authorize FDA inspections, inspections are planned in advance with the foreign firm consenting to FDA inspection. If a firm fails to consent to inspection, FDA considers its options with regard to product approval and entry admissibility decisions."[98]

84. Three FDA compliance programs provide the relevant guidance for the inspections conducted at the ZHP facilities at issue in this matter. FDA's Compliance Program 7346.832 ("CP 7346.832") addresses preapproval inspections ("PAI Inspections");[99] Compliance Program 7356.002F ("CP 7356.002F") sets forth the agency's approach to API process

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95 FDA, *Foreign Inspection Program* (last updated Apr. 27, 2015), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/field-management-directives/foreign-inspection-program.

96 *Id.*

97 *Id.*

98 *Id.*

99 *See generally* FDA, *Compliance Program Guidance Manual: Program 7346.832* ("CP 7346.832"), https://www.fda.gov/media/121512/download.

inspections ("API Inspections");[100] and Compliance Program 7356.002 ("CP 7356.002") addresses drug process inspections "DP Inspections."[101]

85. As CP 7346.832 explains, "[p]reapproval facility evaluations and inspections support the assessment of marketing applications by ensuring that any establishment named in or referenced in support of an application [(i.e., an NDA or ANDA)], can perform the proposed manufacturing operations in conformance with [c]GMP requirements and that data submitted in the application are accurate and complete."[102] PAI inspections have four "inspectional objectives": (1) confirming readiness for commercial manufacturing; (2) confirming conformance to application; (3) conducting a data integrity audit; and (4) confirming a commitment to quality in pharmaceutical development.[103] CP 7346.832 repeatedly refers inspectors to ICH Q7 when conducting PAI inspections involving APIs.[104]

86. The FDA's goal for API Inspections is to ensure that "each API firm will receive biennial inspectional coverage."[105] Inspections are designed to focus on at least two of the following six systems: (1) Quality, (2) Facilities and Equipment, (3) Materials, (4) Production, (5) Packaging and Labeling, and (6) Laboratory Control.[106] The FDA's inspection "program is intended to provide for a risk-based inspection strategy."[107] FDA investigators are instructed that "[i]nspection depth should . . . reflect appropriate risks associated with a particular firm's

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100 *See generally* FDA, *Compliance Program Guidance Manual: Program 7356.002F* ("CP 7356.002F"), https://www.fda.gov/media/75201/download.

101 *See generally* FDA, *Compliance Program Guidance Manual: Program 7356.002* ("CP 7346.002"), https://www.fda.gov/media/75167/download.

102 CP 7346.832 at 11.

103 *Id.* at 13.

104 *See, e.g.*, *id.* at 22-29.

105 CP 7356.002F, at 7.

106 *Id.* at 8-9.

107 *Id.* at 9.

operations, such as the firm's compliance history, the technology employed, the labeled and purported characteristics, and the intended use in the finished product, if known, of the APIs."[108]

87. There are two types of API inspections: surveillance and compliance. As CP 7356.002F explains, "[s]urveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities," while "[c]ompliance inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility for-cause."[109] In addition to surveillance and compliance API inspections, the FDA also differentiates between "full" and "abbreviated" API inspections, either of which may satisfy the FDA's requirement of biennial API inspections.[110] In a full API inspection, an investigator will examine at least four of the six systems listed above, one of which must be the "Quality System."[111] These inspections are designed "to provide a broad and in-depth evaluation of the firm's conformity to [c]GMPs."[112] By contrast, abbreviated API inspections are designed to "provide an efficient update evaluation of the firm's conformity to [c]GMPs" and involve an inspection of "at least two systems but not more than three systems, one of which must be the Quality System."[113]

88. Finally, CP 7356.002 provides the FDA's inspection protocols for drug products – i.e., finished drugs. The protocols contained in CP 7356.002 are designed to "ensure that establishments consistently manufacture drug products of acceptable quality and minimize

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108 *Id.*

109 *Id.* at 10.

110 *Id.* at 12.

111 *Id.*

112 *Id.*

113 *Id.* at 13.

consumers' exposure to adulterated drug products."[114] "Under this compliance program, inspections, investigations, sample collections, sample analyses, and regulatory or administrative follow-up are made to identify quality problems and adverse trends at establishments, so that FDA can develop strategies to mitigate them."[115] Among other things, DP Inspections are designed to "[g]ain insight into the effectiveness of a drug manufacturer's quality system . . . [and] inform [the FDA's] understanding, to the extent possible, of practices at a facility that not only support meeting CGMP compliance requirements to establish and maintain a robust state of control but also promote a quality culture that allows for exceeding this standard."[116] CP 7356.002 inspections are characterized as either "surveillance," which, like CP7356.002F inspections, can be full or abbreviated and are designed to ensure conformity with CGMPs, or "for-cause," in which case the inspection is designed to address a specific FDA concern.[117]

89. All PAI, API, and DP inspections result in an Establishment Inspection Report ("EIR"), which sets forth the inspectors' findings from the audit.[118] The EIR includes "the eNSpect Establishment Inspection Report," the investigator's narrative report, as well as any attachments and exhibits.[119]

90. An EIR is distinct from a Form 483, which "is intended for use in notifying the inspected establishment's top management in writing of significant objectionable conditions, relating to products and/or processes, or other violations of the FD&C Act and related Acts (see

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114 CP 7356.002 at 9, https://www.fda.gov/media/75167/download.

115 *Id.*

116 *Id.*

117 *Id.* at 12-13.

118 *See, e.g.*, CP 7346.832 at 3; CP 7356.002F at 1. *See generally* FDA Office of Regulatory Affairs, FMD 86: Establishment Inspection Report Conclusions and Decisions ("FMD 86") (Jan. 28, 2014), https://www.fda.gov/media/87643/download.

119 FDA, *Investigators Operations Manual 2022*, § 5.11.1, https://www.fda.gov/media/76769/download.

IOM 5.2.3.2) which were observed during the inspection."[120] Observations in a Form 483 are ranked in order of significance.[121] By contrast, an EIR is issued at the end of every inspection, regardless of whether there any negative findings.[122]

91. There are three possible results of an inspection: (1) No Action Indicated ("NAI"); (2) Voluntary Action Indicated ("VAI"), and (3) Official Action Indicated ("OAI").[123] An NAI finding means no objectionable conditions or practices were found during the inspection (or no further regulatory action is warranted).[124] A VAI finding means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action.[125] An OAI finding means regulatory and/or administrative actions will be recommended.[126]

92. Based on my review, it appears ZHP's Chuannan Facility (FEI No. 3003885745)[127] has hosted five FDA inspections since 2010, when the TEA process (without quenching) was introduced. The results of these inspections are briefly summarized below:[128]

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120 *Id.* § 5.2.3.

121 *Id.*

122 *Id.* § 5.11.4.3.1 ("A comprehensive EIR should be prepared for initial inspections as well as foreign inspections in all program areas.").

123 FMD § 6.1.

124 *Id.*

125 *Id.*

126 *Id.*

127 "FEI is an acronym which stands for FDA Establishment Identifier. It is also known as the Firm or Facility Establishment Identifier. The FEI number is a unique identifier assigned by the FDA to identify firms associated with FDA regulated products." FDA, *Glossary: FDA Data Dashboard*, https://www.fda.gov/about-fda/fda-data-dashboard/glossary-fda-data-dashboard#:~:text=FEI%20Number%3A&text=It%20is%20also%20known%20as,associated%20with%20FDA%20regulated%20products (last updated May 26, 2020).

128 FDA, *Zhejiang Huahai Pharmaceutical Co., Ltd. - FEI No: 3003885745*, https://datadashboard.fda.gov/ora/firmprofile.htm?FEIs=3003885745; *see also* (1) SOLCO00153678 (2010 visit EIR); (2) ZHP00107709 (2014 visit EIR); (3) PRINSTON00161863 (2017 visit EIR); (4) ZHP01427917 (2018 visit EIR); (5) ZHP02748824 (2021 visit EIR).

ZHP Chuannan Facility (FEI No. 3003885745)		
Inspection Type	**Inspection End Date**	**Result/Classification**
PAI & API Inspection (Surveillance)	2010.09.08	No Action Indicated (NAI)
API Inspection (Surveillance)	2014.05.23	No Action Indicated (NAI)
PAI & API Inspection (Surveillance)	2017.05.19	Voluntary Action Indicated (VAI)[129]
PAI & API Inspection (For-cause)	2018.08.03	Official Action Indicated (OAI)
API Inspection (For-cause)	2021.07.29	No Action Indicated (NAI)

93. Similarly, it appears ZHP's Xunqiao Facility (FEI No. 3003999190), has hosted ten FDA inspections since 2010, the results of which are briefly summarized below:[130]

ZHP's Xunqiao Facility (FEI No. 3003999190)		
Inspection Type	**Inspection End Date**	**Result/Classification**
PAI & API Inspection (Surveillance)	2010.09.02	No Action Indicated (NAI)
API & DP Inspection (Surveillance)	2013.08.09	No Action Indicated (NAI)
PAI, API & DP Inspection (Surveillance/Abbreviated)	2015.03.27	No Action Indicated (NAI)
PAI Inspection	2016.07.14	Voluntary Action Indicated (VAI)
PAI, API & DP Inspection (Surveillance)	2016.11.18	Voluntary Action Indicated (VAI)
PAI Inspection	2017.06.14	No Action Indicated (NAI)
PAI &DP Inspection	2018.01.27	No Action Indicated (NAI)

[129] According to the EIR of 2018 inspection, the 2017 inspection had been initially classified as OAI and then reclassified as VAI inspection. (ZHP01427917 at 918.)

[130] FDA, *Zhejiang Huahai Pharmaceutical Co., Ltd. - FEI No: 3003999190*, https://datadashboard.fda.gov/ora/firmprofile.htm?FEIs=3003999190; *see also* (1) SOLCO00153737 (2010 visit EIR); (2) PRINSTON00367665 (2013 visit EIR); (3) PRINSTON00112882 (2015 Visit EIR); (4) PRINSTON00081547 (Form 483 from 2016.07 inspection, no EIR available); PRINSTON00081596 (ZHP response to July 2016 inspection); (5) PRINSTON00121802 (Nov. 2016 visit EIR); (6) PRINSTON00115430 (2017 visit EIR); (7) PRINSTON00115443 (2018 visit EIR); (8) ZHP01413994 (May 2019 visit EIR); (9) ZHP01429848 (June 2019 visit EIR); (10) ZHP02748850 (2021 visit EIR).

ZHP's Xunqiao Facility (FEI No. 3003999190)		
Inspection Type	**Inspection End Date**	**Result/Classification**
API & DP Inspection (For-cause)	2019.05.31	Official Action Indicated (OAI)
PAI Inspection	2019.06.28	Voluntary Action Indicated (VAI)
API & DP Inspection	2021.07.02	No Action Indicated (NAI)

94. As noted above, the FDA classified nine of its 15 visits to the ZHP facilities above as "No Action Indicated," four as "Voluntary Action Indicated," and just two as "Official Action Indicated." ZHP did not receive an OAI inspection classification until ***after*** it alerted the FDA that genotoxic impurities had been identified in valsartan API in 2018. In other words, FDA investigators did not any find objectionable conditions or practices that justified regulatory action during the visits to ZHP facilities prior to the identification of nitrosamines in May 2018.

95. For example, while inspecting packaging operations during a July 2016 PAI inspection for Losartan Potassium and Rivaroxaban at the Xunqiao site, an FDA investigator noted that "data is not recorded contemporaneously" after he observed a ZHP operator record three result values from a cap torque removal test at least two minutes after completing the test. (PRINSTON00081547.) That minor procedural deviation was listed first on the two-item Form 483 issued to ZHP at the conclusion of the inspection, meaning it was the most significant finding from the visit, which resulted in a VAI classification.[131]

96. The FDA returned to ZHP's Xunqiao facility in November 2016 and found the following issues warranted VAI classification: (1) failure to follow written procedures designed to prevent contamination of drug products purporting to be sterile; (2) failure to establish

[131] (*Id.*) *See also* FDA, *Investigations Operations Manual 2022*, § 5.2.3, https://www.fda.gov/media/113432/download ("explaining observations [in a Form 483] should be ranked in order of significance").

laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity; (3) failure to implement and follow appropriate procedures for cleaning and disinfecting equipment; and (4) failure to record data contemporaneously. (PRINSTON00121802 at 804.) As with the July 2016 visit examined above, official FDA documentation shows that the observations are actually quite minor and almost entirely unrelated to valsartan API. For instance, the first (and therefore most significant) observation cited in the EIR relates to the manufacturing process for sterile drug products – of which valsartan is not one. (*Id.* at 812.) In fact, at the time of this inspection, the sterile facility at the Xunqiao site was a newly commissioned facility that had not yet made a commercial sterile product for either the domestic or international market. (PRINSTON00115473 at 474.) Thus, in addition to being unrelated to valsartan API, the most significant observation from this inspection is a minor CGMP deviation that did not impact any commercial product.

97. As noted above, the FDA's 2018 for-cause API Inspection at Chuannan was the only inspection of that site resulting in an official action indicated (OAI) rating. The inspection was a "foreign comprehensive For-Cause inspection." (PRINSTON00155822 at 823.) The API Inspection covered four systems: (1) Quality, (2) Facilities and Equipment, (3) Production, and (4) Laboratory Control. (*Id.*) As part of their analysis, the inspectors reviewed "[b]atch production records, laboratory records, training records, logbooks, protocols, procedures, deviation investigations, change control, and stability study data . . . ." (*Id.*) The EIR for the 2018 for-cause API Inspection (the "2018 EIR") noted that a Form FDA 483, Inspectional Observations (the "2018 Form 483"), was issued at the close of the inspection noting a number

of issues at the facility. (*Id.*; *see also* ZHP00061069 (original Form 483 issued on August 3, 2018); ZHP02298856 (amended Form 483 issued on August 8, 2018).)

98. In the 2018 EIR, the investigator documented that he "reviewed the Stability Protocol for Valsartan, USP CS-12-005 implementation date January 11, 2012" and noted that (1) "[a]ll data reported was within specification," and (2) the "[r]esults were similar across U.S. and non-U.S. markets." (*Id.* at 830.)

99. The 2018 EIR noted that ZHP "has an established Quality Unit consisting of the Quality Assurance department and the Quality Control laboratories." (*Id.* at 827.) It further noted that the "firm has established written procedures for the quality unit covering supplier qualification, training, batch release, validation, calibration, investigations including deviations and Out-of-Specification (OOS); product recall, stability studies and complaints." (*Id.* at 827-828.)

100. The inspector "observed employee practices, reviewed documents, and conducted personal interviews with various staff members to assess whether the firm's quality system is designed to achieve sufficient control over the facility and commercial manufacturing operations." (*Id.* at 828.) "Through these activities, [she] observed the Quality Unit is involved in activities including but not limited to: review of manufacturing documents and approval of product prior to release; qualification and validation activities; deviations and investigations; and change control activities." (*Id.*)

101. A large portion of the 2018 EIR was focused on the ongoing investigation following the discovery of NDMA in valsartan API in May 2018. The report noted that at the time of the inspection, July 23, 2018 to August 3, 2018, there was an "[o]ngoing deviation investigation for Deviation Number DCE-18001 [that] was initiated June 6, 2018, for a suspected

genotoxic impurity in Valsartan." (*Id.*) It further noted that the impurity was reported by one of ZHP's customers. (*Id.*) Per the 2018 EIR, "[t]he firm's customer [redacted] informed the firm the customer identified a small unknown peak after the [redacted] peak during residual solvent testing using a GC-FID instrument that led the customer to send samples to a third-party laboratory for identification of the unknown peak (the third-party laboratory identified the unknown peak as NDMA (N-Nitrosodimethylamine))." (*Id.*)

E. Testing/Investigations Of Valsartan API And Manufacturing Process By Finished Dose Manufacturers

102. In addition to the many inspections of ZHP's facilities by international regulatory bodies, ZHP routinely hosted more than 50 customer audits each year. (*See*, *e.g.*, ZHP01523564 at 566.) Based on my review of information submitted to the European Directorate for the Quality of Medicines & Healthcare ("EDQM") in January 2019, from 2016 to late 2018, the Chuannan facility passed all 161 customer audits performed at the site for which it had received results at the time of submission. (*See* ZHP02248202 at 202-204 (email from ZHP to EDQM attaching ZHP02248205); *see also* ZHP02248205 at 206-216.)[132] Indeed, an earlier draft of the same document appears to show that out of the hundreds of customer audits that took place at Chuannan between 2010 and June 2018, ZHP "passed" every customer audit other than two in 2015– an impressive record that belies Plaintiffs' experts' assertions that ZHP was not focused on compliance. (*See* ZHP00835103 at 107-139; Bain Rep. at 16 (asserting "that ZHP's internal quality records confirming CGMP compliance are not reliable").)

103. ZHP generally received positive reviews of its compliance program from its customers' auditors. For example, following Helm AG's audit of the Chuannan site from

[132] At the time the document was prepared, six customer audits were outstanding. (*See* ZHP02248205 at 206.)

September 9-13, 2013, the auditors noted that ZHP was "well organized and in a position to manufacture APIs in accordance with GMP in dedicated workshops and on dedicated plant." (ZHP00383880 at 895.) A third-party audit for Helm in May 2015 also concluded that ZHP performed production and releasing activities for valsartan at a good degree of compliance with EU CGMP standards and recommended that Helm conditionally approve ZHP as a valsartan API manufacturer. (ZHP02465908 at 920-921.) Likewise, when Pinyou Pharmaceutical Co. conducted its audit of Chuannan in June 2017, it concluded that ZHP's "[q]uality management system is set up in accordance with the applicable section of GMP guidelines of CFDA, EU GMP PART-II/ICH Q7us-FDA CFR/WHO, as well as associated ISO guidelines and standards as they related to GMP facility and product compliance." (ZHP00828912 at 919.) It also noted that a "complete documentation system for all kinds of SOPs was on site, and quality management SOPs such as change control, deviation, complaints, CAPA, validation, calibration, self-inspection and product quality review are strictly executed." (*Id.*)

F. Novartis Identification Of Nitrosamines In 2018 And ZHP's Response.

104. On May 21, 2018, Novartis AG contacted ZHP regarding several unknown peaks that it had discovered during the course of its residual solvent testing using a "combined [GC] method." (ZHP02172439.) In its email, Novartis provided ZHP with the chromatograms and requested a response regarding the unknown peaks. (*Id.*)

105. ZHP replied by providing a GC-FID chromatogram identifying one of the unknown peaks at issue as dimethyl sulfide and another unknown peak as the "diluent of residual solvent method." (ZHP00389304 at 307-308.) Novartis expressed uncertainty that the first unknown peak was dimethyl sulfide and asked for data to support ZHP's assessment. (*Id.* at 307.) In response, ZHP ran a GC-MST that did not identify the NDMA. (*See id.* at 306 ("please kindly find the chromatogram of GC-MS & Identification as attached.").)

106. Novartis requested that a third-party laboratory at Solvias AG conduct a further analysis to identify the peaks using gas chromatography-mass spectrometry ("GC- MS") which resulted in the identification of a peak as NDMA. (*See* ZHP00400281 at 281-298.) In a June 6, 2018 email to ZHP, Novartis told ZHP that it wanted "support in understanding if the peak in the Novartis report N-Nitrosodimethylamine is possible" and also noted "[t]his peak should also be seen in the Huahai method but at an earlier retention time." (ZHP00388639 at 645-646.)

107. On June 11, 2018, Novartis confirmed that "N-Nitrosodimethylamine [(NDMA)] is indeed the peak after toluene in our GC analysis." (ZHP01875818 at 822.) In its response, ZHP noted that it would conduct its own analysis "immediately." (*Id.*)

108. On June 18, 2018, Prinston notified the FDA of the discovery of the presence of NDMA in its Valsartan tablets USP. (PRINSTON00068560.) In the same communication, by email and letter, Prinston noted its large market share and the potential to cause a drug shortage in the US market. (*Id.* (letter); ZHP00002079 at 081 (email).) Prinston sought a meeting to ask for the "FDA's guidance and concurrence in terms of how to establish an appropriate acceptance limit of N-nitrosodimethylamine in Valsartan API as well as in its finished products." (PRINSTON00068560.)

109. The letter also noted that no adverse events had been reported regarding ANDA No. 204821 Valsartan Tablets and ANDA No. 206083 Valsartan-HCTZ Tablets, which had been approved on June 9, 2015, and February 9, 2016, respectively. (*Id.*) Nonetheless, the letter explained that ZHP had stopped the release and distribution of the valsartan drug substance. (*Id*.) Prinston had also stopped releasing and distributing both valsartan drug products. (*Id.*) Although Prinston expressed concern that the holds could result in a drug shortage, Prinston ceased distributing product with API sourced from ZHP as of June 18, 2018. (*Id.* at 560-561.)

110. On June 25, 2018, as promised in its initial letter (*id.* at 562), ZHP electronically submitted a "meeting information package." (ZHP00099548 (transmission email); ZHP00099595 (cover letter); ZHP00099567 (information package).) The package included the following information: (1) the background of the event; (2) a summary of ZHP's investigation to date regarding the root cause of the issue; (3) a potential carcinogenic risk assessment; and (4) its plan moving forward. (ZHP00099595 at 596; *see generally* ZHP00099567.)

111. On July 9, 2018, ZHP held a teleconference with the FDA. (ZHP00078092.) Among the attendees was Lisa Oh, Regulatory Project Manager, CDER, Office of Generic Drugs. (*Id.*) Per the meeting minutes prepared by the FDA, "[t]he purpose of [the] teleconference [wa]s to provide clarification of Prinston's risk assessment and proposed plan to minimize NDMA in the drug products Valsartan Tabs and Valsartan-HCTZ." (*Id.* at 093.) The meeting focused on (1) a short-term plan for releasing batches; and (2) an intermediate plan for drug substance reprocessing. (*Id.* at 094.)

112. On July 13, 2018, Prinston publicly announced that it had voluntarily initiated a recall of valsartan products. (SOLCO00000173.) Although the recall was voluntary, Prinston required agreement from the FDA because the recall could cause a major shortage given that Prinston controlled over 50% of the market share for generic valsartan medication. (PRINSTON00068560.)

113. The FDA eventually classified the voluntary recall as a Class II, level A recall (communication to the consumers and 100% recovery of products). (ZHP00111012.) Specifically, in its letter announcing the decision, the FDA explained:

> [The Food and Drug Administration (FDA)] agrees with your firm's decision to recall all lot numbers within expiry, strengths and bottle counts of Valsartan USP tablets. This product is being recalled because a

> carcinogen impurity was detected in the API used to manufacture this product. Your firm initiated this recall on July 13, 2018.
>
> We have reviewed your action and conclude that it meets the formal definition of a "Recall." This is significant, as your action is an alternative to a Food and Drug Administration legal action to remove your defective product from the market. This recall will be reported in an upcoming issue of the weekly FDA Enforcement Report.
>
> * * *
>
> [The] FDA has classified this action as a Class II recall. This means that a situation exists in which the use of or exposure to this violative product may cause temporary or medically reversible adverse health consequences. Our evaluation indicates that this recall be conducted to the Consumer/User level and that level A, effectiveness checks should be conducted by your firm. Level A means that 100% of the total number of consignees needs to be contacted.
>
> In addition to your recall efforts, it is equally important to assure that all returned merchandise, if any, is promptly inventoried, handled, and stored in such a manner as to assure its separation from acceptable materials so it will not inadvertently be used or shipped. Our past experience in similar situations has shown that the longer a defective product is held between the initiation and termination of a recall, the greater the chance of its accidental use.
>
> We request that you advise Recall Coordinator, Ms. Lisa Mathew within ten days of the steps you have taken or will take to ensure that the recalled merchandise is properly inventoried and maintained to prevent unintended use or shipment, and that you provide your proposed corrective actions i.e., method of the disposition of the returned goods or reconditioning.
>
> In addition, we also request that you submit monthly recall status reports to Ms. Lisa Mathew.

(ZHP00111012.)

114. Following its receipt of this letter, ZHP provided the requested monthly updates. (*See, e.g.*, ZHP00110256 (transmitting the first report on August 13, 2018); ZHP00084138 (November status update).)

115. On November 21, 2018, in an email transmitting the monthly update regarding the status of the recall, ZHP informed the FDA that it planned to destroy returned product. (*See*

ZHP00084138 at 138-139.) The FDA approved the decision on November 29, 2018, and ZHP provided proof of destruction of certain recalled valsartan product that had been returned to ZHP on January 11, 2019. (*Id.* at 138.)

116. In addition to its work with the FDA on the recall itself, ZHP also worked with the FDA to provide the regulator with information in connection with the issuance of an Import Alert for ZHP's Chuannan Facility on September 28, 2018 (ZHP00084598 (September 27, 2018 email providing a "complete list of all customers since January 2011 to whom ZHP shipped valsartan API intermediate")) and the FDA's issuance of Warning Letter 320-19-04 on November 29, 2018 (ZHP00393513).

117. On December 26, 2018, ZHP provided its initial response to the Warning Letter in a three-page letter detailing all the work it had done and was doing to correct the issue. (PRINSTON00084798.) On February 6, 2019, the FDA sent ZHP a list of 11 categories of additional information the FDA needed from ZHP to continue its investigation. (ZHP00250032.) This was followed by an email from the FDA to ZHP on March 7, 2019, requesting an expedited response to certain questions related to ZHP's letter of December 26, 2018.[133] (ZHP01510611.) On April 14, 2019, ZHP submitted a response totaling 238 pages in response to the FDA's requests. (*See generally* PRINSTON00158423.)

118. This process of repeated exchanges and the provision of significant information to the FDA continued for nearly two years, until the FDA closed out the Warning Letter on November 4, 2021 after the NAI classified inspection of July 29, 2021. (ZHP02748991.)

[133] Although the FDA's email refers to ZHP's response of "December 6, 2018," it appears this was simply a typo and the FDA official meant to refer to the December 26, 2018 response.

119. In summary, once ZHP learned of the presence of NDMA, it quickly took steps – including through related entity Prinston – to protect the public. The firm informed the FDA, placed all batches on hold, and soon after initiated a recall. It subsequently destroyed recalled product returned to ZHP to ensure that it would not accidently be used and confirmed its destruction to the FDA. The firm also cooperated with the FDA's subsequent investigation, providing it with significant amounts of information.

G. FDA Findings That Neither Regulators Nor Industry Knew Of The Potential For Nitrosamine Formation In The Manufacture Of Valsartan API Prior To May 2018.

120. The FDA is charged with protecting the public. It is a government organization designed to be completely unbiased and independent. The FDA approved the valsartan API manufacturing process, as well as the methods used for testing the drug substance, as part of its review and approval of the ANDA submissions for finished dose valsartan drug products.

121. Following the identification of NDMA in valsartan API in June 2018, the FDA made two public statements confirming that neither the FDA nor the pharmaceutical industry previously had reason to suspect that nitrosamines were present in valsartan API, and that there was no FDA-approved test to detect and quantify nitrosamines in valsartan API or drug products at the time.

122. In the FDA's initial July 13, 2018 press release regarding the identification of NDMA in valsartan API and the resulting voluntary recall of certain valsartan drug products, the FDA stated that "***[t]he presence of NDMA was unexpected*** and is thought to be related to changes in the way the active substance was manufactured."[134] The FDA noted that it would

[134] https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.

"continue to investigate this issue and provide additional information when it becomes available."[135] A little over a month later, on August 30, 2018, FDA Commissioner Dr. Scott Gottlieb issued a more detailed statement explaining that:

> In St. Louis, the FDA maintains the most advanced pharmaceutical laboratory of any regulatory agency in the world. As soon as we were aware of the NDMA impurity in certain valsartan drugs, we began collecting samples of all valsartan API and products marketed in the U.S. ***At the same time, our scientists began developing a test to detect and quantify NDMA in valsartan API. NDMA's properties make it difficult to find.***
>
> * * *
>
> To determine if valsartan products do contain this impurity, ***CDER's scientists have now developed the gas chromatography-mass spectrometry (GC/MS) headspace testing method***. We posted this method to the web to help manufacturers and regulators detect NDMA in valsartan API and tablets.
>
> * * *
>
> After assessing information about ZHP's manufacturing processes and the changes ZHP made over time, we identified how its processes could have led to the presence of NDMA in their API.
>
> Specifically, a combination of conditions, which include certain chemicals, processing conditions and production steps, could lead to formation of the NDMA impurity. We believe that these risks are introduced through a specific sequence of steps in the manufacturing process, where certain chemical reactions are needed to form the active ingredient. ***Before we undertook this analysis, neither regulators nor industry fully understood how NDMA could form during this process.*** We are still not 100 percent sure that this is the root cause of the problem. Full understanding will require correlation of multiple test results from valsartan APIs made by different processes with the various process steps used by different manufacturers or at different times.[136]

123. In his August 2018 statement on behalf of the FDA, Dr. Gottlieb went on to expressly note that "***[b]ecause it was not anticipated that NDMA would occur at these levels in***

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135 *Id.*

136 *See* https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current (emphasis added).

the manufacturing of the valsartan API, manufacturers would not have been testing for it" and regulatory investigators would not know to look for it.[137] The FDA also stated that: "[o]ne challenge we've faced is that NDMA's properties make it hard to detect in standard laboratory testing – the kind of testing results that are reviewed during a surveillance inspection."[138] These challenges were echoed by experts in the field, who have noted that, prior to 2018, scientists did not have testing methods that could detect very small amounts of NDMA or NDEA.[139]

124. On January 25, 2019, eight months after the initial identification of NDMA in valsartan API and more than five months after the FDA's inspection of the Chuannan facility, Dr. Gottlieb issued a further updated official statement on behalf of the FDA noting that the regulator was "making important strides at understanding how these impurities occurred, mitigating the risk to patients and learning what steps need to be taken to prevent this from occurring again in the future."[140] In the January 2019 statement, the FDA explained the steps that it takes to ensure compliance with CGMPs for drugs products and substances, including "inspect[ing] manufacturing facilities worldwide" and reviewing "impurity testing" data.[141] The FDA expressly noted that:

> Tests are selected based on assessments of what impurities may develop as a result of the manufacturing process. In other words, ***it generally needs to be recognized that there's a risk of an impurity occurring as a result of a manufacturing process to know the impurity should be tested for***.[142]

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137 *Id.* (emphasis added).

138 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

139 https://cen.acs.org/articles/98/i15/NDMA-contaminant-found-multiple-drugs.html.

140 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

141 *Id.*

142 *Id.* (emphasis added).

125. According to the January 2019 statement, the FDA's "investigation into ZHP's process identified that a change made to the manufacturing process likely led to this impurity, and that the impurity went undetected by global regulators, including the FDA, for a period of time.[143] ***Before we undertook this analysis, neither regulators nor industry fully understood how NDMA or NDEA could form during this particular manufacturing process***."[144]

126. The January 2019 statement also acknowledged that "it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API"[145] and "[i]t's unlikely that the subtle problems causing these impurities could have been found on a routine current good manufacturing practice (CGMP) inspection."[146] This view is shared by experts in the field, who have noted that scientists did not know to look for NDMA or NDEA in drugs prior to its identification in valsartan in 2018.[147]

127. Neither the FDA nor industry detected the potential for nitrosamine despite the FDA's thorough review of drug manufacturing processes in connection with the FDA-approval process, which the FDA detailed in both its August 2018 and January 2019 statements.[148]

128. According to the FDA in August 2018:

> We review [information about impurities that may be introduced or develop during manufacturing processes] in product applications, including requests to change the manufacturing process. We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality,

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143 *Id.*

144 *Id.* (emphasis added).

145 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

146 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

147 https://cen.acs.org/articles/98/i15/NDMA-contaminant-found-multiple-drugs.html.

148 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current; https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

> to review applications and referenced information to look for steps – and manufacturing changes – where these risks could be introduced.[149]

129. Further, in the January 2019 statement, the FDA explained "the many steps [it] take[s] to mitigate" the risks of impurities in FDA-approved drugs, specifically noting that the regulator "engage[s] experts in organic chemistry to detect circumstances that can create the risk for these kinds of impurities to be introduced as a by-product of the manufacturing process or changes made in that process."[150] FDA "***chemists review applications and referenced information to look for steps and changes where risks could be introduced.***"[151] This statement recognizes that, consistent with general FDA procedures set forth above, experienced, expert chemists employed by the FDA would have reviewed the information related to the valsartan API manufacturing process changes at issue, which were detailed in the Drug Master File for valsartan API, when reviewing ANDAs for valsartan products containing the API. (*See* PRINSTON00019190 at 190-193; PRINSTON00037447 at 448-450.) None of the expert FDA chemists expressed any concerns about the TEA with quenching process or the Zinc Chloride process at any point prior to ZHP's June 2018 self-report of NDMA in valsartan API.

130. Both the August 2018 and January 2019 FDA statements also included an assessment of the theoretical risk that the amount of NDMA identified in valsartan API posed to patients, which the FDA characterized as "extremely low."[152]

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149 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

150 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

151 *Id.* (emphasis added).

152 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current; https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

131. As the FDA explained: "CDER toxicologists and chemists evaluated the risk to the public" to estimate "the theoretical risk that the impurity could pose to patients."[153] The FDA

> Estimated that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time [the FDA] believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people beyond the average cancer rate among Americans.[154] This estimate represented the highest possible level of NDMA exposure. It was a measure of the risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario.[155]

132. The FDA made similar statements in January 2019, including:

> Our analysis of NDMA found that the risk to patients based on the maximum possible exposure appears to be small.
>
> * * *
>
> While consumers should limit exposure to NDMA and NDEA, these impurities exist in other ingested products, such as some charcoal grilled food items. And so, our goal is to balance the risk of patients ingesting low levels of the impurities (below the interim acceptable levels) for a short period of time with the risk that there is a shortage of certain ARBs, which may impact patients' ability to access the medicine they need.
>
> * * *
>
> Overall, the risk to individual patients remains very small, although this doesn't diminish the significance of this episode or our concerns. FDA scientists estimate that if 8,000 people took the highest daily valsartan dose (320 mg) that contained NDMA, for four years (the time we think the affected products had been on the U.S. market), there may be one additional case of cancer beyond the average cancer rate among those 8,000 Americans. The vast majority of patients exposed to NDMA through ARBs

153 *Id.*

154 *Id.*

155 *Id.*

received much smaller amounts of the impurity than this worst-case scenario.[156]

133. In short, the FDA has recognized that the trace amounts of nitrosamines identified in valsartan API do not present a significant risk to the public.

VI. ZHP COMPLIED WITH REGULATORY REQUIREMENTS IN THE MANUFACTURE AND SALE OF VALSARTAN API.

134. Contrary to Plaintiffs' experts' assertions, ZHP complied with CGMP and ICH standards in manufacturing and selling valsartan API.

135. ***First***, ZHP conducted appropriate risk assessments of each of the relevant changes to the API manufacturing process (TEA with quenching and Zinc Chloride) based on what was known at the time those manufacturing changes were made. ZHP also disclosed the content and results of those assessments to the FDA for review and approval through the ANDA process. The FDA did not express any concerns about these manufacturing processes, much less express concerns that either of the manufacturing processes was capable of causing the formation of NDMA or NDEA. To the contrary, after nitrosamines were identified in valsartan API in May 2018, the FDA repeatedly stated that ***neither industry nor regulators were aware*** that NDMA or NDEA could form during the manufacture of valsartan API prior to May 2018. (*See* Section V.G, above.)

136. ***Second***, ZHP conducted appropriate testing of its valsartan API consistent with applicable USP standards. The FDA was aware that ZHP tested its valsartan API using the GC-FID chromatography and did not have any concerns with that approach. Further, applicable FDA guidance makes clear that ZHP was not required to identify impurities below 0.10% of the weight of the valsartan API within a given tablet – e.g., less than 0.32 mg in a 320 mg valsartan

[156] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

tablet.[157] Plaintiffs' experts have not presented any evidence that valsartan API contained nitrosamines above 0.10% and therefore should have been identified by ZHP. Nor have Plaintiffs' experts presented any evidence that, prior to May 2018, ZHP knew of the potential for nitrosamine impurities in valsartan API such that it would have had reason to go beyond industry testing standards and use GC-MS testing to identify unknown impurities below 0.10%. In addition, FDA inspections and observations related to the manufacture of valsartan API prior to May 2018 were generally positive, indicating that both ZHP and the regulator believed that ZHP was manufacturing and testing its API in conformance with CGMPs. (*See* Section V.D, above.)

137. ***Third***, ZHP responded appropriately to the discovery of nitrosamines in valsartan API in May 2018, including by enacting a voluntary recall and withdrawing all valsartan API from the United States market. Plaintiffs' experts rely heavily on findings in FDA inspection reports and Warning Letters issued ***after*** nitrosamines were identified in valsartan API that document observations regarding ZHP's manufacturing and testing processes. But these documents are routine regulatory tools used to record observations of potential compliance issues and encourage action by industry members. They are not official findings of noncompliance with CGMPs. The FDA's findings were issued ***after*** valsartan API was recalled based on knowledge not available to industry or regulators prior to 2018 – and ZHP ultimately resolved the issues raised to the FDA's satisfaction. As a result, these FDA communications cannot establish non-compliance with CGMPs at the time valsartan was being marketed and sold. (*See* Section V.F, above.)

138. ***Fourth***, Plaintiffs' experts lack support for the assertion that generic valsartan API was adulterated at the time of sale because it was not bioequivalent to the brand-name RLD,

[157] ICH Q3A, at 8, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf.

Diovan. Whether a pharmaceutical drug is adulterated is a determination made by the FDA; a drug cannot be retroactively deemed adulterated for purposes of litigation. Moreover, the presence of trace impurities in a generic drug or drug component does not affect bioequivalence or render a drug adulterated. And in any event, an independent lab (whose nitrosamine testing has been reviewed and confirmed by Dr. Najafi) identified NDMA ***in Diovan***. Thus, even if bioequivalence were affected by trace impurities, Plaintiffs' experts' theories would still be illogical.

A. ZHP Conducted And Disclosed Appropriate Risk Analyses Of The Zinc Chloride And TEA With Quenching Processes Consistent With CGMPs And Regulatory Requirements.

139. Plaintiffs' experts generally opine that ZHP failed to comply with CGMPs in manufacturing valsartan API because it did not conduct a proper risk assessment of the TEA with quenching and Zinc Chloride manufacturing processes. (*See, e.g.*, Bain Rep. at 1, 15, 18, 21, 59; 2022 Najafi Rep. at 27-29; Plunkett Rep. at 30-31, 35; Hecht Suppl. Rep. at 2-4, 7.) As set forth above, however, ZHP performed lengthy, thorough investigations of these processes before submitting the manufacturing changes to the FDA to analyze potential risks, including an investigation of the potential for impurities.

140. While Plaintiffs' experts point to various conduct by ZHP that they claim is evidence of technical CGMP violations, their overall complaint is that ZHP did not perform a proper risk assessment because the company did not specifically investigate whether either of these processes was capable of causing the formation of nitrosamines such as NDEA and NDMA. (*See, e.g.*, Bain Rep. at 19-23, 74; 2022 Najafi Rep. at 3, 27-29; Plunkett Rep. at 30-31, 35; Hecht Suppl. Rep. at 2.) For example, Dr. Najafi opines that ICH Q7 requires API manufacturers to demonstrate that their manufacturing process is not at risk for forming nitrosamines, including by adding a purification step and additional testing if needed, and ZHP

violated CGMP by failing to do so. (Najafi 2022 Rep. at 3.) Dr. Najafi also opines that ICH Q10 requires that manufacturers verify that their synthetic process can routinely make the drug substance without forming nitrosamines. (*Id.* at 9.) Similarly, Dr. Plunkett opines that ZHP violated CGMP by "not conducting a full risk assessment related to nitrosamine decomposition products formed during the TEA and the $ZNCl_2$ processes." (Plunkett Rep. at 31; *see e.g.*, Hecht Suppl. Rep. at 2 (proper risk assessment "would have required testing for NDMA and NDEA of each batch of drug product manufactured with both processes"); Bain Rep. at 74 ("technology to test for nitrosamine impurities existed, was well known, and should have been applied to determine whether nitrosamines were forming").) This is incorrect.

141. As an initial matter, the FDA and ICH regulations and guidance in place prior to the discovery of NDMA in valsartan API in May 2018 did not require ZHP to test its products for NDMA or NDEA specifically. Instead, as described in Section IV, above, relevant guidance and regulations relevant to CGMP for API manufacturers required investigation of impurities that were reasonably expected to occur in the manufacture of a drug substance. Indeed, the FDA has expressly stated that "it generally needs to be recognized that there's a risk of an impurity occurring as a result of a manufacturing process to know the impurity should be tested for."[158] The FDA has also made clear that "[t]o implement a risk assessment for any genotoxic impurity, ***there must be recognition that it can occur in a product's manufacturing***."[159] As explained in detail in the report of Fengtian Xue, ZHP's scientists did not have a reasonable scientific basis to expect that NDMA or NDEA could form during either the TEA with quenching or Zinc Chloride

[158] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

[159] *Id.* (emphasis added).

processes; thus, ZHP did not have a reason to investigate nitrosamines at the time the company was performing its risk assessments for these processes. (*See* Xue Rep. at Section V.B.2.)

142. The adequacy of ZHP's risk assessments is confirmed by the regulatory history of valsartan API. As set forth above, ZHP properly documented its changes to its manufacturing processes through the submission of: (1) Drug Master File Amendment-002, which detailed the TEA with quenching process change, in April 2012; and (2) Drug Master File Amendment-004, which detailed the Zinc Chloride process change, in December 2013. The FDA never expressed any concerns regarding the processes as detailed in the Drug Master Files, let alone concern that either process might lead to the formation of nitrosamines.

143. Plaintiffs' experts do not dispute that a Drug Master File amendment is the appropriate vehicle for a pharmaceutical substance manufacturer to inform the FDA of a change to its manufacturing process. Nevertheless, Plaintiffs' experts, including Bain and Plunkett, assert that ZHP's Drug Master File amendments were insufficient to alert the FDA to review the TEA with quenching and Zinc Chloride processes because the FDA does not independently review Drug Master Files and neither approves nor disapproves them. (*See* Plunkett Rep. at 15 ("In other words, FDA does not 'approve' a Drug Master File submission, or a change or amendment to a Drug Master File."); *see also* Bain Rep. at 51.) This is incorrect. The very regulations cited by Plaintiffs' experts make clear that Drug Master File submissions and amendments related to an API are reviewed in connection with ANDAs submitted for the drug products that incorporate the API.[160] As a result, the Dug Master File submissions related to the TEA with quenching and Zinc Chloride processes were reviewed by the FDA in connection with

[160] *See, e.g.*, 21 C.F.R. § 314.420(a); https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs (cited in Plunkett Rep. at 14).

any ANDA for a valsartan drug product filed after the Drug Master File, including Prinston's ANDA 204821 for its valsartan product, which was approved by the FDA on June 9, 2015. (SOLCO00025625 at 025-027.)

144. As noted above, the FDA made repeated official statements clarifying that, prior to the identification of NDMA in valsartan API in 2018, it had taken a number of steps to ensure the safety of ANDA-approved valsartan medications, including employing robust teams of organic chemists to "review applications and referenced information to look for steps and changes where risks could be introduced."[161] And, as evidenced by the FDA's 2011 letter to ZHP identifying issues with a Drug Master File for a prior iteration of the valsartan API not at issue in this case, the FDA does not hesitate to raise questions or concerns about the information in an API Drug Master File in reviewing ANDA submissions for finished products. (*See* PRINSTON00171741 at 741-743 (FDA stating that its approval of Torrent's ANDA for a valsartan drug product in 2011 "was contingent upon adequate information being provided in a supporting [Drug Master File]").)

145. The fact that none of the FDA chemists who reviewed ANDA applications for valsartan products (and the Drug Master Files for valsartan API encompassed therein) expressed any concerns over the TEA with quenching or Zinc Chloride manufacturing processes undermines Plaintiffs' experts' assertion that "[k]nowledge of basic organic chemistry suggests that changes to the chemical reagents of a reaction would alter the degradant/by-product profiles requiring such risks to be critically evaluated" and that ZHP was therefore required to conduct a

[161] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps; *see also* https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current ("We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality, to review applications and referenced information to look for steps – and manufacturing changes – where these risks could be introduced").

"risk-based evaluation of the possible formation of nitrosamines resulting from their proposed process changes." (2022 Najafi Rep. at 27; *see also id.* at 7 ("Basic chemistry principles instruct us that secondary amine in the presence of nitrite and acid predictably and readily react to produce genotoxic nitrosamines such as NDMA and NDEA"); Bain Rep. at 74 ("The potential chemical reactions leading to the creation of nitrosamines were well understood, and should have been considered from the outset and throughout.").) If Plaintiffs' experts were correct that any chemist should have known, as a matter of basic chemistry, that the TEA with quenching and Zinc Chloride processes were likely or even capable of causing nitrosamine formation, the expert chemists at the FDA would have been aware of these risks and flagged them in their valsartan ANDA reviews. There is no evidence anyone at the FDA had this concern prior to the identification of NDMA in valsartan in May 2018. To the contrary, the FDA publicly stated in January 2019, after conducting a months-long analysis regarding the potential formation of nitrosamines in connection with the valsartan API manufacturing process, that "[b]efore we undertook this analysis, neither regulators nor industry fully understood how NDMA or NDEA could form during this particular manufacturing process."[162]

146. Plaintiffs' experts focus on the Zinc Chloride process, which uses DMF as a solvent. According to these experts, it has been widely known since at least 1996 that DMF can degrade into dimethylamine, which can react with sodium nitrite plus hydrochloric acid to form NDMA. (*See* 2022 Najafi Rep. at 26 ("Using DMF solvent in the process should have raised concern for the possible formation of nitrosamines because DMF solvent has been long known to decompose into dimethylamine."); *see also* Hecht 2022 Rep. at 5; Bain Rep. at 2; Plunkett Rep,

[162] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps. (emphasis added).

at 34-35.) But DMF Amendment-004, which was submitted in December 2013 and would have been reviewed in connection with the Prinston ANDA application approved in June 2015, clearly states that the Zinc Chloride manufacturing change involves the addition of DMF as a solvent to Step 4 of the manufacturing process to facilitate the reaction in that step. (PRINSTON00073102 at 104.) If Dr. Najafi and Plaintiffs' other experts were correct that ZHP chemists should have known to test for NDMA in valsartan API based solely on the use of DMF, FDA chemists would have known this as well and raised a concern about it. They did not. And even ***after*** NDMA was identified in valsartan, the FDA publicly acknowledged that it was not obvious that NDMA would form from the Zinc Chloride manufacturing process, stating that "NDMA's properties make it difficult to find."[163]

147. Plaintiffs' experts opine that ZHP and valsartan drug product manufacturers hindered the FDA's review of these manufacturing process changes by describing them as "minor" changes to the FDA after ZHP internally classified the changes as "critical." (*See, e.g.*, Bain Rep. at 24, 69; Plunkett Rep. at 15.) This assertion, too, is baseless. ZHP's internal procedure for approving the manufacturing changes at issue was managed through the company's Change Control system, as outlined in ZHP's Standard Management Procedure ("SMP")-018. (*See* ZHP00469139; ZHP01839729.) Section 6.2.1 of SMP-018 provides that proposed changes must be classified as "critical" or "minor" for purposes of internal review. (*See id.*) Pursuant to the SMP, a "critical change" would include any "change which has direct or potential impact on product identity, strength, quality, purity and ***regulation, or have impact on validated procedure***, method, qualification of equipment." (*Id.* (emphasis added).) By

[163] *See* https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

contrast, a "minor change" would be limited to changes that have "negligible or no impact on product identity, strength, quality and purity." (*Id.*) These are internal ZHP designations and definitions, not regulatory classifications.

148. As ZHP explained to the FDA in 2018, as part of its response to the FDA's 483 observations following its for-cause inspections of ZHP's facilities after the discovery of NDMA in Valsartan API, the primary reason why the Zinc Chloride manufacturing process change was internally classified as "critical" was that the change involved the alteration of the phase transfer catalyst in the crude product step, switching from triethylamine as catalyst to zinc chloride, as well the introduction of new solvents, DMF and MTBE. (*See* ZHP02579954 at 041.) These changes qualified as "critical" pursuant to ZHP's internal SMP-018 designations because they needed to be reported to the FDA through amendment to the Drug Master File and therefore would have an effect on "regulation" and "validated procedure[s]." (*See* ZHP00469139; ZHP01839729.) Contrary to Plaintiffs' experts' suggestion, there is no indication that this internal designation pursuant to the requirements of SMP-018 was due to the fact that ZHP believed that the changes would have an effect on drug quality or purity.

149. Further, regardless of whether ZHP subjectively designates changes to its manufacturing processes as "critical" or "minor," the appropriate mechanism to report these changes was through the Drug Master File Amendment process, which ZHP used. (*See, e.g.*, PRINSTON00000005 at 008-009.) And regardless of how ZHP described its manufacturing process change in the Drug Master File amendment, the FDA would have applied the same standards in reviewing the Drug Master File in connection with reviewing the ANDAs submitted for valsartan drug products.

150. ZHP also properly disclosed the changes to the Zinc Chloride and TEA with sodium nitrate valsartan processes to finished dose manufacturers. (*See, e.g.*, PRINSTON00132152, PRINSTON00132154; ZHP00417442, ZHP00417443, ZHP00417454.) Indeed, a 2018 email from Torrent to ZHP notes that ZHP provided Torrent with a Change Notification in 2012, informing Torrent of the Zinc Chloride process change. (*See* ZHP00417442.) The email attaches two Change Notifications that explain the process change in detail. (*See* ZHP00417443, ZHP00417454.) The first page of these Change Notifications specifically states: "Solvent change: In manufacturing processes of step 3 and step 4, DMF and MTBE is added to facilitate the process." (ZHP00417454.) The Change Notifications go on to detail and illustrate the ROS for each step of the Zinc Chloride process, noting how DMF is used in the process, including that both DMF and sodium azide (NaN_3) would be used in Step 4 of the process. (*Id.* at 459.) These Change Notifications demonstrate that ZHP informed valsartan drug product manufacturers of the change to its manufacturing process, disclosed the addition of DMF to the process, and explained that DMF would be present with a sodium azide, which Plaintiffs' experts suggest was well-known to result in the production of NDMA. (*See* 2022 Najafi Rep. at 27-28.)

151. Plaintiffs' experts have not identified any evidence that ZHP's finished dose customers, after being alerted to the specific changes in the manufacturing processes at issue, raised concerns regarding the potential formation of nitrosamines. Nor is there any evidence that these manufacturers of valsartan drug products suspected that the changes increased the risk of nitrosamine formation such that a CBE or PAS was warranted. This is strong evidence that the industry as a whole – like the FDA – did not have a reasonable basis at the time to suspect that either the Zinc Chloride or the TEA with sodium nitrate quenching process was capable of

causing the complex chemical reactions necessary to cause NDMA or NDEA. Accordingly, Plaintiffs' experts lack a legitimate basis for the position that any qualified chemist should have known that certain aspects of the process changes (i.e., the potential for degradation of the DMF added in the Zinc Chloride process, or the possibility of a reaction between TEA and sodium nitrite in the TEA with quenching process) could result in the formation of nitrosamines.

152. Plaintiffs' experts suggest that the failure to identify NDMA in valsartan API during ZHP's risk assessment process for the Zinc Chloride process was particularly egregious – even "likely criminal" – in light of the "unusually potent" nature of the impurity. (*See* Bain Rep. at 73; Plunkett Rep. at 4.) For instance, Dr. Plunkett states that "there is no controversy surrounding the fact that [NDMA] is a potent carcinogen; an increased cancer risk is associated with exposure to nanogram levels of NDMA." (Plunkett Rep. at 4.) This is contrary to the FDA's determination that the risk to patients from NDMA or NDEA at the levels found in valsartan API would be extremely low.[164] As explained above, FDA scientists estimated that:

> [I]f 8,000 people took the highest daily valsartan dose (320 mg) that contained NDMA, for four years (the time we think the affected products had been on the U.S. market), there may be one additional case of cancer beyond the average cancer rate among those 8,000 Americans. The vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario.[165]

153. Moreover, a federal judge recently found that the plaintiffs in litigation involving allegations of NDMA in another pharmaceutical drug "fail[ed] to produce admissible primary evidence" that trace amounts of NDMA in pharmaceuticals are capable of causing cancer. *In re*

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164 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

165 *Id.*

Zantac (Ranitidine) Prod. Liab. Litig., No. 20-MD-2924, 2022 WL 17480906, at *167 (S.D. Fla. Dec. 6, 2022). Among other things, the court explained that:

> None of the Plaintiffs' experts have provided reliable primary evidence of dose-response relationship for ranitidine. The Plaintiffs' experts either fail to address dose-response relationship or provide dose-response relationship opinions derived from unreliable methodologies. Furthermore, the Plaintiffs' experts have not provided reliable opinions regarding what threshold dose of NDMA causes each of the five Designated Cancers, let alone what threshold dose of ranitidine causes cancer. Based upon the totality of the evidence, none of the Plaintiffs' experts provided reliable primary evidence of a dose-response relationship for ranitidine and the Designated Cancers. The lack of reliable dose-response relationship opinions casts doubt on the reliability of the Plaintiffs' experts' general causation methodologies.

Id. at *158.

154. Plaintiffs' experts also contend that company witnesses admitted in their depositions that ZHP did not perform an adequate analysis of its manufacturing process changes or conduct appropriate risk analyses. (*See, e.g.*, Bain Rep. at 27-30, 33-37, 41-43, 51; Plunkett Rep. at 30-31.)

155. For example, Bain repeatedly states that company witnesses conceded that ZHP failed to properly assess potential impurities that could result from the manufacturing process changes. (*See, e.g.*, Bain Rep. at 27 (asserting that Eric Gu, President/General Manager of the ZHP-related entity Shanghai Syncores, confirmed that no genotoxic impurity analysis was completed when developing the zinc chloride process); *id.* at 28 (opining that Dr. Gu agreed that ZHP inadequately evaluated impurities resulting from chemical reactions).) According to Bain, this alleged failure to assess potential impurities not only violated CGMPs, but also other relevant regulatory standards, including the FDA Guidance "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches," EMA guidelines titled "Guideline on the Limits of Genotoxic Impurities," and various ICH provisions. (*See, e.g.*, Bain

Rep. at 27, 28, 30, 36.) These opinions misstate the relevant testimony and ignore the significant testing performed by ZHP as part of the risk assessment process.

156. Dr. Gu made clear at his deposition that ZHP conducted a risk assessment of the Zinc Chloride process based on the relevant regulations, including ICH guidelines, in place at the time. Specifically, Dr. Gu testified that, in developing the Zinc Chloride process and testing it in the laboratory setting, Shanghai SynCores completed "thorough studies" in compliance with ICH and other guidelines. (4/5/21 Gu Dep. at 74-76; *see also id.* at 99 (testifying that SynCores did "whatever possible with our knowledge base at that time" in conducting the risk assessment for the process change); *id.* at 249-51 (explaining that SynCores "did a solvent screening for many different solvents" as part of its risk assessment, followed CGMPs and ICH guidelines, and ultimately got approval from the FDA and EDQM).)

157. Other company witnesses, including Peng Dong of ZHP's Technical Department, similarly testified that ZHP "conducted [an] impurity analysis and risk assessment based on the requirements of laws and regulations, which included the risk assessment on genotoxic impurities." (4/1/21 Dong Dep. 368; *see also* 3/30/31 Dong Dep. at 156 ("During the valsartan zinc chloride process change in 2011, the technical department conducted evaluation of DMF as the additional solvent and added testing for residual DMF in the quality specification."); *id.* at 189 (explaining that his department conducted a risk assessment for the change procedure, including "materials and parameters change," in 2011).)

158. Indeed, Bain herself acknowledges that company witnesses confirmed that "evaluation of potential quality or purity issues with introducing DMF into the zinc chloride process was conducted by the technical department, quality assurance department, quality

control department, including personnel with chemistry background." (Bain Rep. at 34 (citing 3/30/21 Dong Dep. 153-158).)

159. Bain's opinion that ZHP failed to properly assess potential impurities resulting from the manufacturing process changes in violation of CGMPs and other regulatory standards is also contradicted by the regulatory history of valsartan. As noted above, ZHP conducted extensive research and testing for more than two years to ensure that valsartan API met expected standards, including for genotoxic and other impurities. (*See* Paragraphs 154-157, above.) The impurity profile of the drug substance was evaluated both before and after the process change, and this included an evaluation of potential genotoxic impurities. (*See, e.g.*, ZHP01843066 at 099; ZHP01710663 at 0697; ZHP01710792 at 835-940 (annex 2 to ZHP01710663 setting forth analysis of potential genotoxic impurities in valsartan).) As set forth above, amendment-004 to DMF No. 023491 (disclosing the Zinc Chloride process change) provided testing results showing that no single unknown impurity detected exceeded .03% and that the total impurities, excluding impurity A, which is irrelevant here as discussed above, ranged from .04% to .09%. (PRINSTON00073102 at 119.) Thus, ZHP concluded that "[t]here [was] no adverse change in qualitative and quantitative impurity profile" and "the process change /optimization [had] not impact[ed] drug quality." (*Id.* at 113.)

160. Bain references testimony from various witnesses – including Dr. Gu and Dr. Min Li (Vice-President for ZHP Analytical Operations) – acknowledging that ZHP did not specifically test for nitrosamines in connection with ZHP's process changes. (*See, e.g.*, Bain Rep. at 33 (the process validation described by Mr. Dong "failed to include testing for nitrosamine"); *id.* at 29 (suggesting that Dr. Gu should have known "to test to try to identify potential nitrosamine impurity"); *id.* at 35 (Mr. Dong "confirmed that ZHP did not do any

investigation into the potential for DMF to decompose and yield dimethylamine until June 2018"); *id.* at 36 ("Mr. Dong confirmed that the risk assessment . . . 'did not identify the potential risk of nitrosamine impurity in valsartan.'").) But ZHP concedes that the company did not specifically investigate the potential for nitrosamines in its API prior to May 2018.[166] As detailed throughout this report, this does not constitute a CGMP violation because neither ZHP, nor manufacturers of finished dose valsartan products, nor the FDA had a reasonable scientific basis to suspect that nitrosamines could form as a result of ZHP's manufacturing processes.

161. The European Medicines Agency's ("EMA's") "Guideline on the Limits of Genotoxic Impurities," which Bain cites in her report (*see, e.g.*, Bain Rep. at 28, 37, 40), underscores this point. Broadly speaking, the EMA Guideline "describes a general framework and practical approaches on how to deal with genotoxic impurities in new active substances."[167] In particular, the EMA Guideline provides an approach to assessing exposure to genotoxic impurities: (1) that have a known dose-response relationship such that exposure levels without appreciable risk can be established (section 5.1); and (2) that do not have sufficient evidence to establish an acceptable level of exposure and therefore require a policy of completely eliminating the impurity or controlling impurity levels to "as low as reasonably practicable" where avoiding it is not possible (section 5.2).[168] Critically, the EMA Guideline applies only to impurities that "might reasonably be expected based on knowledge of the chemical reactions and conditions

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166 *See* Stipulation of Zhejiang Huahai Pharmaceutical Co., Ltd., ¶ 3(e) (May 13, 2022).

167 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-limits-genotoxic-impurities_en.pdf. This EMA Guideline was superseded by ICH M7.

168 *Id.*

involved."[169] In addition, the EMA Guideline makes clear that "no action is generally required" where such impurities are "found at levels below the ICH identification threshold."[170]

162. Relatedly, Bain also contends that company witnesses admitted that it was ZHP's responsibility to "fully evaluate the impurities" as part of its ongoing risk management of valsartan API. (Bain Rep. at 31.) Bain criticizes ZHP's purported failure to investigate unknown peaks, opining that "it was unacceptable for ZHP to ignore" those impurities and that the failure to identify the cause of the unknown peaks "constituted a violation of CGMP." (Bain Rep. at 30; *see also id.* at 39 (stating that Dr. Min Li "confirmed a stream of complaints from customers . . . regarding unknown peaks").)

163. But ZHP did not "ignore" unknown peaks at all. To the contrary, ZHP conducted a number of tests designed to identify the impurities. As noted above, the Drug Master File Amendment for the Zinc Chloride process change provided detailed testing results for impurities with no single unknown impurity exceeding the threshold at which it had to be identified: 0.10%. (*See* PRINSTON00073102 at 118-119.)

164. In any event, Plaintiffs' experts have not identified any unknown peaks reported to ZHP that were above the FDA threshold of 0.10% for unknown impurities.[171] As Dr. Gu correctly explained, "the FDA, ICH guideline clearly specifies if [the unknown peak] is below 0.1 percent, you don't have to qualify, quantify." (4/5/21 Gu Dep. 234.) And while Dr. Gu noted that ZHP always endeavored "to gain an understanding of all those unknown peaks in any drug substance," he correctly acknowledged that it is "almost impossible" to do so for every

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169 https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-limits-genotoxic-impurities_en.pdf.

170 *Id.*

171 *See* https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf.

impurity. (4/5/21 Gu Dep. 235.) The FDA recognizes this, which is why the 0.10% regulatory threshold for the identification of potential impurities exists.

165. There is also no basis for Plunkett's suggestion that ZHP acted inconsistently with CGMPs because the FDA has stated that "if a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe." (Plunkett Rep. at 21.) Plaintiffs' experts have not identified any evidence demonstrating that the impurity levels for valsartan API increased overall following either of the manufacturing changes at issue or that there were new impurities above the FDA threshold of 0.10%. To the contrary, as noted above, ZHP's testing showed that unknown impurities remained under the 0.10% threshold. (PRINSTON00073102 at 118-119.) For this reason, too, ZHP would not have had reason to believe that the Zinc Chloride or TEA with sodium nitrate quenching process could cause the formation of dangerous impurities that needed to be investigated.

166. Bain also points to Dr. Li's deposition testimony regarding an ICH Guideline titled "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7." (Bain Rep. at 40-41.) A plain reading of the scope of that guideline makes clear that ICH M7 only applies to "new drug substances and new drug products during their clinical development and subsequent applications for marketing," as well as to "new marketing applications and post approval submissions for marketed products."[172] Dr. Li made the same observation at his deposition, noting that "the degradants that we discuss here or the [M7] discuss here [are] typically related to after the making of a drug substance" and that degradation that may occur during the API manufacturing process is "outside the scope" of M7. (4/21/22 Li Dep. 386-87.) More importantly, ICH M7 became effective in May 2015, years after

[172] M7(R1), at II, https://www.fda.gov/media/85885/download.

the process changes at issue.[173] The guideline itself notes that it is "not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guidance)."[174] Thus, ICH M7 is irrelevant to ZHP's CGMP compliance in assessing the risks of the process changes at issue.

167. Plaintiffs' experts also contend that company witnesses admitted that ZHP short-circuited its analysis of its manufacturing process changes in violation of CGMP guidelines. For example, Bain asserts that ZHP did not conduct "a scale up process from lab scale to pilot scale to commercial scale" for its manufacturing process change. (Bain Rep. at 26; *see also id.* at 33 (suggesting Mr. Dong agreed a pilot scale study was required for manufacturing changes).) But, as Dr. Gu explained, ZHP used commercial scale studies in lieu of pilot scale studies given the company's history and familiarity with manufacturing valsartan API and in light of the fact that the process change only involved changing the catalyst used in the crude step. (4/6/21 Gu Dep. 415-416.) In other words, as Dr. Gu testified, instead of first testing the revised manufacturing process on a slightly smaller scale before enlarging the scale, ZHP was able to "use the commercial scale as the technical batch to replace the pilot scale." (4/6/21 Gu Dep. 421-424.)

168. Contrary to Bain's suggestion, this approach does not violate CGMP principles. The purpose of laboratory or pilot scale studies is to predict the performance of the commercial scale process and ensure that a manufacturer has assurance that the manufacturing process will consistently produce API that meets the expected standards relating to identity, strength, quality, purity, and potency. Smaller-scale studies are designed to be representative of the commercial scale process and are used to estimate commercial-scale results. But the commercial scale

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[173] M7(R1), at 1 & n.1, https://www.fda.gov/media/85885/download.

[174] M7(R1), at IV, https://www.fda.gov/media/85885/download.; *see also* M7(R1) at Appendix 1 ("Retrospective application of the M7 Guidance is not intended for marketed products unless there are changes made to the synthesis. [If] no changes are made to the drug substance synthesis, the drug substance would not require reevaluation.").

process is always the most ideal for assessing the manufacturing process and product quality. As Dr. Gu made clear in his testimony, where possible, it is "better to use larger scale to do studies than the pilot scale, because from pilot scale to commercial scale, things still can change." (4/6/21 Gu Dep. 424.)

169. Bain also asserts that ZHP's evaluation of the substances involved in the manufacturing process change was insufficient because ZHP "only evaluated the amount of residual sodium azide and sodium nitrate." (Bain Rep. at 33.) But, as Mr. Dong explained, this was because both sodium azide and sodium nitrate had been used before the process change, and ZHP concluded through the risk assessment process that the increased amounts of those substances did not significantly increase the potential risk of residual sodium azide and sodium nitrate. (3/30/21 Dong Dep. 221-22.) Moreover, even though ZHP had concluded that the potential risk was low, it still conducted testing to determine the residual amounts of those substances and performed a further risk assessment based on that testing, which was guided by the ICH requirements at that time. (3/30/21 Dong Dep. 222-24.)

170. In short, Plaintiffs' experts' opinions that ZHP failed to conduct a proper risk assessment for its TEA with quenching and Zinc Chloride process changes because the company did not specifically investigate whether NDMA or NDEA could form during these processes are baseless. The realities of what was known at the time these processes were developed demonstrate that ZHP did not have a reasonable basis to test for nitrosamines in its API. After the identification of trace amounts of nitrosamines in valsartan API in May 2018, the FDA publicly stated that industry can only test for impurities, including potential genotoxic impurities,

that are recognized as occurring in the product.[175] The FDA also recognized that neither the pharmaceutical industry nor the FDA was aware of the potential for NDMA or NDEA in valsartan because the properties of these nitrosamines make them hard to find.[176] This is consistent with the documented regulatory history of the TEA with quenching and Zinc Chloride processes. (*See* PRINSTON00000005 at 005-006; PRINSTON00236649; PRINSTON00251397.) Both processes were detailed in Drug Master File amendments to the FDA, which were reviewed and approved by the regulator in connection with subsequent ANDAs for finished dose valsartan drug products. (*Id.*; PRINSTON00019190 at 190-193; PRINSTON00037447 at 448-450.) ZHP also issued Change Notifications to the manufacturers of valsartan drug products explaining the details of the process changes. (*See, e.g.*, PRINSTON00132152; PRINSTON00132154; ZHP00417442; ZHP00417443; ZHP00417454.) To my knowledge, neither the FDA nor any ZHP customer raised any issue with the aspects of ZHP's manufacturing processes that Plaintiffs' experts now claim were well-known to result in nitrosamine formation (such as the potential degradation of DMF used in the Zinc Chloride process or, separately, the quenching step of the TEA with quenching process). Thus, there is no legitimate basis to conclude that ZHP violated CGMPs by not specifically testing for these unexpected impurities.

171. Plaintiffs' experts also contend that ZHP violated CGMPs by failing to properly clean the equipment on certain production lines, resulting in cross-contamination that introduced NDMA into valsartan API. (*See, e.g.*, Bain Rep. at 20-21, 59, 74; 2022 Najafi Rep. at 27; Hecht 2022 Rep. at 2.) As explained in detail in ZHP's November 2018 Deviation Investigation

[175] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

[176] *Id.*

Report, which detailed ZHP's investigation of nitrosamine formation in valsartan API, a number of ZHP's valsartan production lines were dedicated to single manufacturing processes, such that no cross-contamination would have occurred. (ZHP02563327 at 547.) In addition, the production lines on which different manufacturing processes were used were subject to proper cleaning processes pursuant to the company's written standard operating procedures for equipment cleaning, which were based on the scientific information available at the time and were validated by testing. (*Id.* at 470, 525, 547-548.) Because ZHP did not have reason (prior to May 2018) to suspect that NDEA or NDMA could result from any of its manufacturing processes for valsartan API, it also did not have reason to know that the cleaning procedures it used between changes in manufacturing processes needed to be able to remove NDMA and/or NDEA from the equipment. (*Id.* at 548.) As a result, ZHP did not violate CGMPs by failing to develop and use cleaning procedures specifically designed to eliminate NDMA and/or NDEA. Again, compliance with CGMPs turns on what is reasonably known at the time product manufacturing takes place – not information that becomes available after the manufacturing conduct has stopped. Finally, as of November 2018, ZHP confirmed that all production lines for valsartan API had been retrofitted and replaced and there was no future potential for cross-contamination. (*Id.* at 548.)

B. ZHP Performed Appropriate Testing Pursuant To Regulatory Requirements And CGMPs While Valsartan Was On The Market.

172. Several of Plaintiffs' experts fault ZHP for analyzing valsartan API by means of gas chromatography with flame-ionization detection ("GC-FID"), which was the industry standard prior to the discovery of NDMA/NDEA in valsartan API in May 2018, taking the position that ZHP should have used gas chromatography-mass spectrometry ("GC-MS"). (*E.g.*, 2021 Hecht Rep. at 20; 2022 Najafi Rep. at 12; Bain Rep. at 13, 71-72.) One of Plaintiffs'

experts even goes so far as to assert that, as of May 2018, the GC-MS method was "well-established" in the industry. (Bain Rep. at 62.) These opinions are baseless.

173. ZHP developed methods for analyzing valsartan in 2007. For residual solvents that might be carried over from process to product – the category into which NDMA or NDEA would fall – a headspace GC-FID (or "HS-GC/FID") method was developed. (*See* ZHP01661736.)

174. Headspace GC is a sample preparation method for determining volatile compounds in solid and liquid samples. Through sample preparation activities, the volatile solvents evaporate into a sealed headspace. An aliquot of this gas-phase sample is removed from the headspace and introduced into a gas chromatograph. "Residual solvent determination in pharmaceuticals is most commonly performed using headspace capillary gas chromatography (GC) with flame ionization detection (FID), a robust technique that incorporates a mode of detection noteworthy for its sensitivity and wide dynamic range."[177] Furthermore, the current USP chapter on residual solvents (USP<467>) specifies GC-FID for detection of residual solvents.[178]

175. DMF was introduced as a solvent in the Zinc Chloride process. (PRINSTON00073102 at 104.) Since it was present as a solvent, it was a fair assumption that some of it could be present in the final product. HS-GC/FID was suited to detect the presence of DMF because it is volatile and would evaporate into the headspace. ZHP's development team

[177] J. Kay et al., Simultaneous *quantitation of water and residual solvents in pharmaceuticals by rapid headspace gas chromatography with thermal conductivity detection (GC-TCD)*, J. Pharm Biomed Anal. 2021 Feb 5; 193:113796. Doj: 10.1016/j.jpba.2020.113796, https://pubmed.ncbi.nlm.nih.gov/33288344.

[178] USP, <467> Residual Solvents (2022), at §§ 7-8.

thus anticipated that DMF was a potential impurity and used HS-GC/FID as the analytical method to detect such impurities. (ZHP00007221 at 233-234.)

176. By contrast, as set forth above, there would have been no expectation that the processes used to synthesize valsartan API would generate trace amounts of dimethylamine, which could lead to formation of NDMA via secondary reaction under special circumstances (in the presence of nitrous acid). (*Id.* at 234.) After all, there had been no literature indicating that NDMA was a potential impurity in valsartan API prior to June 2018. (*Id.*)[179]

177. HS-GC/FID remains one of the techniques commonly used for detecting and measuring residual solvents. ZHP developed its HS-GC/FID method in accordance with the USP monograph on valsartan, validated it, and reported it to the FDA as part of the Drug Master File, which was approved as part of ANDAs for valsartan drug products, as noted in Section V.B, above.

178. Moreover, the United States Pharmacopeia ("USP") stipulates analytical methods and sets specifications for products.[180] By statute, manufacturers need to follow the approved USP testing methodology, or provide justification for using an in-house method (which needs to be demonstrated to be equal or superior to the USP method).[181] Thus, if a product meets the USP

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[179] YM Alshehri et al., *HS-SPME-GC-MS as an alternative method for NDMA analysis in ranitidine products*, J Pharm Biomed Anal. 2020 Nov 30;191:113582. doi: 10.1016/j.jpba.2020.113582, https://pubmed.ncbi.nlm.nih.gov/32889348/ (noting in 2020 that NDMA had been "accidentally discovered in drugs[] such as valsartan" only recently).

[180] *See, e.g.*, USP 35, Chemical Tests (2012), <467> Residual Solvents, at 185, 189-92 (setting forth testing procedures for residual solvents); USP 35, Official Monographs (2012), at 4997-98 (setting limits on impurities in valsartan).

[181] 21 U.S.C. § 351(b) (providing that drugs that are listed in "an official compendium," which is elsewhere defined to include (as relevant here) the USP, "determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium" subject to exceptions not relevant here); https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-control-components-and-drug#14 (clarifying that methods equal or superior to the compendial method may be used, but "in the event of a dispute, the compendial method is considered conclusive").

testing requirements, it is compliant with statutory requirements.[182] In the timeframe at issue, the USP-prescribed testing method for residual solvents was GC-FID.[183]

179. ZHP and Prinston complied with the testing procedures prescribed by the USP – and those testing procedures were disclosed to and approved by the FDA in connection with ANDAs for valsartan drug products. Thus, both ZHP and manufacturers of valsartan drug products complied with their statutory testing obligations.

180. Even if there were an obligation to employ different testing methods from those set forth in the USP, Plaintiffs' experts have failed to identify a basis for their assertion that CGMPs required ZHP to use GC-MS testing. Some of Plaintiffs' experts refer to ICH Q3A, but it is not applicable for the reasons set forth above and, in any event, does not require the use of GC-MS testing. As noted above, ICH Q3A "is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state."[184] By its own terms, it does not apply to an established drug, which will be subject to specifications established in the USP.[185]

181. Nor did ICH Q3A require use of GC-MS to test for NDMA/NDEA prior to June 2018. ICH Q3A provides that an applicant for new drug approval:

> should summari[z]e the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be

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182 *Id.*

183 USP 35, Chemical Tests (2012), <467> Residual Solvents, at 185, 189-92; *see also <467> Residual Solvents*, *Pharmacopeial Forum*, Vol. 33(3) (May–June 2007) (proposing new chapter "Residual Solvents").

184 ICH Q3A (R2) at 3, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-3-r2-impurities-new-drug-substances-step-5_en.pdf.

185 *Id.*

> limited to those impurities that might ***reasonably be expected*** based on knowledge of the chemical reactions and conditions involved.[186]

The applicant is also directed to describe testing used to detect impurities,[187] which presumably would be calibrated to those that were reasonably expected to be present. Reasonably expected impurities would not include NDMA or NDEA because, as discussed above, and as expressly acknowledged by the FDA and other scientists, such impurities were ***not*** expected to be present in valsartan API or produced by the processes at issue.[188]

182. ICH Q3A also calls for the use of analytical procedures that are "validated and suitable for detection."[189] But GC-MS was not validated or shown to be suitable for the detection of NDMA/NDEA prior to May 2018. To the contrary, it was only after May 2018 that the FDA's Office of Testing and Research reported that it "ha[d] developed a gas chromatography-mass spectrometry (GC/MS) headspace method to detect the presence of NDMA and NDEA in valsartan drug substances."[190] That development was sufficiently groundbreaking that the FDA thought it worthy of a press release, reporting that "NDMA's properties make it hard to detect in standard laboratory testing," but that FDA scientists at its St. Louis facility, where "the FDA maintains one of the most advanced pharmaceutical laboratories of any regulatory agency in the world," had "***developed*** and refined ***novel*** and sophisticated

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186 *Id.* at 4 (emphasis added).

187 *Id.*

188 For that reason, although ICH 3QA directs that "analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold," *id.* at 4, that proviso would not be implicated because NDMA and NDEA were not expected impurities.

189 *Id.* at 5.

190 https://www.fda.gov/media/117843/download. Although the documents cited here are dated January 2019, it appears they are updated versions of announcements the FDA initially made in late August 2018. *See* https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

testing methods specifically designed to detect and quantify NDMA and NDEA in all ARB medicines," including "the (GC/MS) headspace method."[191]

183. Even after the FDA's announcements, articles appeared in the literature acknowledging the need for the development and validation of GC-MS techniques for detecting NDMA and NDEA in valsartan and other drug substances. One of those articles noted that NDMA "was accidentally discovered in drugs, such as valsartan and ranitidine."[192] Another – published in 2021 – explained that until the present time, "the determination of N-nitrosamines in APIs through LC-MS/MS and/or GC-MS/MS [had not been] well understood."[193] A 2019 article explained that "none of the pharmacopoeias tests for NDMA and only very limited publications of methods for its determination in pharmaceuticals are published so far," highlighting a 2018 publication of Abdel-Tawab et al. that reported on a GC-MS-based methodology and noting that "no further details of the method [were] currently reported."[194] A later 2019 article explained that, in the wake of the German Regulatory Agency's July 2018 suspension of the marketing authorization for generics containing valsartan, "it became quickly evident that methods to determine NDMA in tablets are urgently needed which lead the Central Laboratory of German Pharmacists (ZL) to develop a suitable GC-MS method for NDMA

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191 https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps (emphases added).

192 YM Alshehri et al., *HS-SPME-GC-MS as an alternative method for NDMA analysis in ranitidine products*, J Pharm Biomed Anal. 2020 Nov 30;191:113582. doi: 10.1016/j.jpba.2020.113582.

193 J Liu et al., *Development of a sensitive and stable GC-MS/MS method for simultaneous determination of four N-nitrosamine genotoxic impurities in sartan substances*, J Anal Sci Technol 12, 3 (2021). doi: 10.1186/s40543-020-00254-2, https://jast-journal.springeropen.com/articles/10.1186/s40543-020-00254-2.

194 Maria Parr and Jan Joseph, *NDMA impurity in valsartan and other pharmaceutical products: Analytical methods for the determination of N-nitrosamines*, 164 J Pharm. Biomed Anal. 536, 537 (2019). Doi 10.1016/j.jpba.2018.11.010, https://www.sciencedirect.com/science/article/abs/pii/S0731708518319861.

quantification within a short period."[195] At the time, no pharmacopeial or official analytical method existed for nitrosamine detection.[196] "This was the first GC-MS method applied for the determination of NDMA in valsartan finished pharmaceutical products. Until then only very limited analytical methods using packed GC columns in combination with TEA (thermal energy analyzer) were published for the determination of NDMA in pharmaceuticals."[197]

184. Plaintiffs' experts have not shown otherwise. Indeed, elements of Plaintiffs' experts' criticisms of ZHP (as well as other members of industry) for their alleged failure to use GC-MS only serve to highlight that use of GC-MS to detect NDMA/NDEA was far from "established," and certainly was not the industry standard or a prevailing CGMP. Bain's evidence that the GC-MS method was "well-established," for example, is that Novartis's identification of NDMA in valsartan API was made possible by that method. (Bain Rep. at 62.) But as Bain acknowledges in the same assertion, Novartis had to involve a third-party contract laboratory to access that technology, reflecting the fact that utilization of GC-MS was not routine. (*Id.*) Bain's report similarly acknowledges that, by April 2019, ZHP had not yet "completed method development for" its more advanced GC-MS/MS instrument to be used to analyze nitrosamines, consistent with evolving FDA regulations and guidance. (Bain Rep. at 61-62.) Bain styles this as a criticism of ZHP for not acting expeditiously, but there was no "off the

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195 F. Sörgel et al., *The contamination of valsartan and other sartans, part 1: New findings*, 172 J Pharm Biomed Anal. 395, 396 (2019), doi: 10.1016/j.jpba.2019.05.022, https://www.sciencedirect.com/science/article/abs/pii/S0731708519302183?via%3Dihub.

196 *Id.* at 401.

197 *Id.* at 396; *see also* W. Wichitnithad et al., *Development of a Sensitive Headspace Gas Chromatography–Mass Spectrometry Method for the Simultaneous Determination of Nitrosamines in Losartan Active Pharmaceutical Ingredients*, 6 ACS Omega J. 11048, 11048 (2021). doi 10.1021/acsomega.1c00982, https://pubs.acs.org/doi/10.1021/acsomega.1c00982 ("Since July 2018, the US FDA, EMA, and other national regulatory agencies have released various methods for the determination of nitrosamine contaminants in sartan APIs based on gas chromatography coupled to mass spectrometry (GC–MS) or tandem mass spectrometry (GC–MS/MS), high-performance liquid chromatography with ultraviolet detection (HPLC–UV), and liquid chromatography coupled to mass spectrometry (LC–MS) or tandem mass spectrometry (LC–MS/MS).").

rack" method for GC-MS testing that would allow for the identification of NDMA/NDEA in valsartan API, even almost a year after the recall. Finally, Najafi states that "ZHP as well as the finished dose manufacturers using ZHP API failed to recognize that the testing of valsartan drug substance must include testing for nitrosamines using GC-MS or LCMS to detect impurities like NDMA and NDEA." (2022 Najafi Rep. at 12.) Again, this complaint only highlights that GC-MS analysis was not standard in the industry and therefore could not sensibly be described as a requirement of CGMP.

185. Plaintiffs' experts nevertheless insist that ZHP should have employed GC-MS analysis based upon its observation of aberrant peaks found using the GC-FID analysis. (*E.g.*, Hecht Rep. at 23; 2022 Najafi Rep. at 32.) But the applicable USP did not direct such follow-up testing.[198]

186. As discussed above, ICH Q3A would not have applied to valsartan API during the time period at issue because valsartan was not then a "new drug."[199] But even if it had, it would not have compelled inquiry into the "aberrant peaks" referenced by Plaintiffs' experts. ICH Q3A expressly provides that "[i]dentification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary,"[200] and the identification threshold for unknown impurities (like the aberrant peaks) was 0.10%, a threshold that the aberrant peaks did not exceed.[201]

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198 *See* USP 35, Official Monographs (2012), at 4997-98.

199 ICH Q3A (R2) at 3, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-3-r2-impurities-new-drug-substances-step-5_en.pdf.

200 *Id.* at 4.

201 *See id.* attachments 1 and 3. Attachment 1 to ICH 3QA indicates that the threshold for identification of an impurity for drugs with a maximum daily dose of 2 g or less is 0.10% or 1.0 mg per day intake, whichever is less. (The maximum daily dose of valsartan is 320 mg. *See* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283.) And *(cont'd)*

187. For these reasons, it is my opinion that ZHP relied on proper testing techniques, and neither ICH Q3A nor prevailing good manufacturing practices dictated resort to GC-MS as argued by Plaintiffs' experts.

C. ZHP Properly Responded To Identification Of Trace Amounts Of Nitrosamines In Valsartan API.

188. ZHP also promptly and properly reported its finding of NDMA/NDEA in valsartan API and took appropriate action consistent with FDA regulations and relevant guidance documents.

189. As explained in Section V.F, above, Novartis first inquired about the identity of unknown peaks found in valsartan API in May 2018. ZHP's documents indicate that it worked quickly with Novartis to identify those peaks and confirmed their identity as NDMA in mid-June 2018. (*See* ZHP01875560.) Within one week, Prinston had reported the issue to the FDA with significant detail. (*See* ZHP00100866; ZHP00100870.) In the same letter, Prinston requested an "urgent teleconference or face-to-face meeting," noting literature identifying NDMA as a possible carcinogen and flagging for the agency the potential implications for valsartan supplies given ZHP's large market share. (*See* ZHP00100866; ZHP00100870.)

190. Plaintiffs' experts do not suggest (nor could they) that ZHP failed to move swiftly following Novartis's inquiry in May 2018. Instead, they dispute that ZHP was unaware that NDMA was or could be present in valsartan API, suggesting that ZHP knew of the potential for nitrosamine impurities as early as July 2017, based on an internal email from Jinsheng Lin that was originally written in Chinese. (*E.g.*, Bain Rep. at 1, 15.) But as detailed in the report of Fengtian Xue, an expert chemist with native fluency in Chinese, Plaintiffs' experts misread this

attachment 3 clarifies that where an impurity is not greater than its identification threshold, no further action is required.

highly technical email. (*See* Xue Rep. at Section VI.) As Dr. Xue explains, the email does not establish ZHP's awareness of a potential for the formation of NDMA or NDEA as a result of the valsartan API production processes, but instead addresses the potential for entirely different impurities in different drug substances. (*Id.*)

191. ZHP was put on notice that there was something to investigate with respect to nitrosamines in valsartan API for the first time in May 2018. (ZHP00359171 at 173.) The company began investigating immediately and less than a month later reported its findings to the FDA through Prinston, which alerted the FDA to the possibility that product interruption might be necessary and have an impact on patients. (*See* Section V.F, above.) ZHP's expeditious investigation and reporting were consistent with FDA regulations and guidances.[202]

192. ZHP also conducted the recall of all affected products consistent with FDA regulations and guidance documents.[203] As summarized above, the company first worked in concert with the FDA to determine whether a recall was appropriate under the circumstances, with particular attention to the potential risk of carcinogenic exposure on the one hand and the potential disruption of valsartan supply on the other. (*See* Section V.F.) The recall was initiated on July 13, 2018 at the consumer level, again reflecting swift action, coming only four days after meeting with the FDA to determine the recall strategy and classification.[204] Thereafter, the FDA

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202 FDA Q3A, https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf; FDA Q7, https://database.ich.org/sites/default/files/Q7%20Guideline.pdf; FDA Q10, https://database.ich.org/sites/default/files/Q10%20Guideline.pdf; 21 C.F.R. § 7.3(k)(1).

203 21 C.F.R. §§ 7.1-7.59; FDA Q7, https://database.ich.org/sites/default/files/Q7%20Guideline.pdf.

204 21 C.F.R. §§ 7.3(k)(1).

indicated that it "agree[d] with [ZHP's] decision" to effectuate a voluntary recall under the circumstances.[205]

193. Plaintiffs' experts offer no criticism of the recall; nor do they suggest that any aspect of the recall failed to comply with applicable regulations or guidances. To the extent they address the recall, it is only to suggest that it should have happened earlier. (*E.g.*, Plunkett Rep. at 32-33.) This suggestion is based on the presumption that NDMA/NDEA impurities should have been discovered earlier, which is incorrect for all of the reasons disussed above.

194. Plaintiffs' experts also generally point to the FDA's observations in a Form 483 and a Warning Letter issued after NDMA/NDEA was identified in valsartan API, suggesting that these documents constitute formal findings of violations of regulations or CGMPs by the FDA. (*E.g.*, Bain Rep. at 63 (asserting that FDA 483s and Warning Letter in 2019 "demonstrate[] that ZHP was in a state of significant cGMP non-compliance").) But these observations by the FDA do not constitute final, binding determinations as to CGMP.[206] Instead, they created an obligation for ZHP to engage with the FDA and take action,[207] which it did in accordance with applicable regulations and guidances, as ultimately reflected in the FDA's determination that the steps taken by ZHP were satisfactory. (ZHP02748991.)

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[205] The recall was appropriately limited to valsartan. As the FDA noted in the EIR summarizing the inspection at Chuannan from July 23 to August 3, 2018, the "[m]anufacturing suites and equipment used in the manufacture of Valsartan, USP [were] dedicated." (PRINSTON00155822 at 827.) Because no other APIs or other drug products were produced using those suites or equipment, nothing but the valsartan could have been affected by the nitrosamines produced by that manufacturing process, and there was no need for ZHP/Prinston to expand the recall beyond valsartan.

[206] FDA, *Form 483 Frequently Asked Questions*, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions, accessed 12/14/2022 ("The FDA Form 483 does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations").

[207] *Id.*

195. First, these communications from the FDA are not final, binding decisions. The Form 483 includes an express disclaimer regarding its contents: "This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. . . ." (*E.g.*, ZHP00061069; ZHP01413880.) The Form 483s at issue here include the same language. (*E.g.*, ZHP00061069; ZHP01413880.)

196. A Warning Letter represents the next enforcement step beyond an observation made in a Form 483. A Warning Letter may be issued in the event the FDA feels that a regulated entity has not responded adequately to the observations set forth in a Form 483, or it may be issued notwithstanding assurances of corrective action in response to a Form 483 to "ensure that the seriousness and scope of the observed violations are understood by top management."[208] As with Form 483s, the FDA expressly states that Warning Letters are not final or binding: "A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit the FDA to taking enforcement action. For these reasons, FDA does not consider Warning Letters to be final agency action on which it can be sued."[209]

197. Second, and relatedly, both Form 483s and Warning Letters are intended to provide the receiving entity an opportunity to respond to the observations they contain and work collaboratively with the FDA toward a consensual resolution.[210] In other words, a receiving entity does not act improperly by failing to concede or capitulate to every observation made in a

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208 FDA, Regulatory Procedures Manual § 4-1-3, at 6 (June 2022), https://www.fda.gov/media/71878/download.

209 *Id. at* § 4-1-1, at 2 (June 2022), https://www.fda.gov/media/71878/download.

210 https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions, accessed 12/14/2022

Form 483 or Warning Letter without question. To the contrary, Form 483 observations are "presented and discussed with the company's senior management" and a written response is expected.[211] The FDA similarly contemplates that recipients of Warning Letters will provide a response for the Agency to consider in deciding on next steps.[212] Ultimately, the purpose of both mechanisms is to spur voluntary corrective action.[213] Thus, absent indication that the responding entity "has been unable or unwilling to correct the [claimed] violations," escalation to formal enforcement action is not warranted.[214]

198. While Plaintiffs' experts point to responses ZHP made to the FDA's Form 483 and Warning Letter as somehow indicative of misconduct or as evidence of non-compliance (*e.g.*, 2022 Najafi Rep. at 30; Bain Rep. at 49-50, 60-62), their opinions misperceive the significance of those Agency communications. ZHP was permitted to challenge certain observations rather than agree with them and suggest corrective action. Similarly, the fact that initial responses to FDA inquiries were deemed by the Agency to be inadequate is not indicative of a finding of a regulatory violation. Provided that the recipient is engaging constructively with the FDA, resolution of observations in a Form 483 or Warning Letter is an inherently collaborative and sometimes iterative process and in the nature of a dialogue, not the unilateral imposition of the FDA's will.

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211 https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions, accessed 12/14/2022.

212 FDA, Regulatory Procedures Manual § 4-1-8, at 15-17 (June 2022), https://www.fda.gov/media/71878/download.

213 https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions, accessed 12/14/2022; FDA, Regulatory Procedures Manual § 4-1-1, at 1 (June 2022), https://www.fda.gov/media/71878/download.

214 FDA, Regulatory Procedures Manual § 4-1-8, at 18 (June 2022), https://www.fda.gov/media/71878/download.

199. Ultimately, the FDA "closed out" its Warning Letter, expressly stating in the close-out letter that "it appears that [ZHP] ha[s] addressed the deviations contained in th[e] Warning Letter." (*Id.*) Close-out letters are not issued lightly; rather, they are issued only where "corrective actions [] actually have been made and verified by the FDA."[215] In other words, ZHP actually demonstrated to the FDA's satisfaction that it was in compliance with the applicable regulations and had resolved the FDA's concerns previously set forth in the Warning Letter and the Form 483 issued post-recall.

200. Third, Plaintiffs' experts seize on the FDA's statements in the post-recall Form 483 and Warning Letter as indicative of alleged compliance failures ***prior*** to the recall, but these opinions constitute textbook examples of hindsight judgments. (*See, e.g.*, 2022 Najafi Rep. at 29-30.) In essence, they seek to hold pre-recall practices to a standard that could only fairly be imposed after the recall, and CGMP does not operate in that fashion.

201. For instance, Najafi highlights the finding in the Form 483 issued on August 3, 2018 that the "change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate" because ZHP did "not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or API." (2022 Najafi Rep. at 29-30.) But the reference in the Form 483 to the "potential impact" of the process change is obviously a reference to the production of NDMA and NDEA impurities (the possibility of which was first discovered in May 2018), not an abstract concern of the FDA about the change or the formality of ZHP's risk assessments. (ZHP00061069.)

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215 *Id.* at 16.

202. This is an unfair post-hoc criticism, whether leveled by Najafi or the FDA. As an initial matter, ICH Q9 states that it is not always appropriate or "necessary to use a formal risk management process."[216] Moreover, at the end of the same month in which the FDA issued the Form 483, it told the public that "neither regulators nor industry fully understood how NDMA could form during this process," and they were "still not 100 percent sure that this is the root cause of the problem" at that time.[217] The FDA conceded the same lack of knowledge during the pre-recall period in a similar statement made five months later, adding that the issue was a "subtle problem" that would have escaped standard CGMP inspections.[218] These statements reflect the reality that CGMP as it was applied during the pre-recall period did not call for testing for NDMA/NDEA impurities (as explained in Section V.A, above). That reality did not change simply because a new understanding of NDMA/NDEA impurities occurred immediately prior to the 2018 recall. As noted in Section VI, it simply is not the case that CGMP categorically requires formal risk assessment.

203. In any event, ZHP responded to this observation by explaining that it did have formal procedures in place (including risk assessment) for proposed changes in its response letter to the FDA. (*See* ZHP02579954.) Nothing in the FDA's correspondence provides a basis to conclude that ZHP's risk assessment was inadequate or insufficiently formal under prevailing CGMP standards.

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[216] ICH Q(9), at 3, https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf.

[217] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current.

[218] https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

204. The FDA's September 28, 2018 Import Alert, which suspended the shipment of ZHP products from the Chuannan facility into the United States, similarly does not establish non-compliance with CGMPs prior to the identification of NDMA in valsartan. (*See, e.g.*, Bain Rep. at 52 58; 2022 Najafi Rep. at 36.) The Import Alert was issued months after ZHP voluntarily recalled its valsartan API from the United States market, and thus did not affect or halt the shipment of ZHP's valsartan products to the U.S. Nor did the Import Alert contain backward-looking conclusions that ZHP had failed to comply with CGMP in connection with the manufacture and testing of valsartan API in the preceding decade. (ZHP00061080.) Instead, the Import Alert was the result of the FDA's observation that the manufacturing processes at the Chuannan facility in 2018 "do not appear to conform to good manufacturing practice" given what had been discovered that year regarding the potential formation of nitrosamine impurities. (*Id*.) As a result, shipments of various medications from Chuannan were suspended to allow ZHP to investigate, make changes warranted by the then-current state of scientific knowledge, and "demonstrate the drugs manufactured at this site, and intended for the U.S. market, are in compliance with CGMP." (*Id.*) Over the next few years (a period that was drawn out due to travel restrictions from the COVID-19 epidemic), ZHP was able to demonstrate compliance with currently-applicable CGMPs, and the import alert was lifted in November 2021. (*See* ZHP02748824; ZHP02748792; ZHP02748807.)

205. In short, ZHP complied with applicable FDA regulations and guidance in connection with reporting the finding of NDMA/NDEA to the FDA, its initiation of a recall of the affected valsartan API, and its responses to the FDA's Form 483, Warning Letter, and Import Alert.

D. ZHP's API Was Not Adulterated.

206. 21 U.S.C. § 351(a)(2)(B) states that a drug will be deemed "adulterated" if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."[219]

207. Plaintiffs' experts argue that the valsartan at issue was adulterated because it did not satisfy CGMP standards and because the generic medication does not match the RLD. (*See, e.g.*, Bain Rep. at 2, 19, 21, 51, 63, 73-75; Plunkett Rep. at 4-5, 41-42.) Dr. Plunkett also argues that the valsartan at issue did not "meet the quality and purity characteristics which it purport[ed], or [wa]s represented, to possess and therefore would be deemed adulterated." (Plunkett Rep. at 12-13.)

208. These opinions misstate FDA regulations in several ways. First, contrary to Dr. Plunkett's mischaracterization, the statute does not say that a drug that does not meet "quality and purity characteristics" is adulterated; it states that the product must be manufactured in conformity with CGMPs that are intended to assure those characteristics.[220]

209. Second, Dr. Plunkett's use of the phrase "would be deemed adulterated" is very telling. (Plunkett Rep. at 12-13.) Adulteration is an FDA finding, not a state of being. For example, when the FDA finds a CGMP violation, it may make a determination that a product

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219 21 U.S.C. § 351(a)(2)(B).

220 *See* 21 U.S.C. § 351(a)(2)(B) ("A drug or device shall be deemed to be adulterated [. . .] if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.").

was adulterated.[221] Thus, a product is not adulterated unless and until the FDA says so. The first time the FDA sent ZHP a Warning Letter related to CGMP was in 2018, ***after the valsartan recall***. (ZHP00393513.) There was no observation of CGMP noncompliance that could result in a finding of adulteration prior to that time. Thus, no valsartan was sold in an adulterated state.

210. Third, the FDA's CGMP observations were made in hindsight, in an effort to determine how the nitrosamine contamination eluded so many scientists and regulators. Newer information not available while a product was on the market cannot retroactively render a product adulterated.

211. Fourth, Plunkett is also wrong in her second key opinion, where she states that the valsartan at issue was not "the generic equivalent of the FDA-approved branded drug listed in the Orange Book" because "NDMA and NDEA are harmful impurities that are not listed under the branded pharmaceutical in the US Pharmacopeia (USP) valsartan monograph or the applicable valsartan FDA applications Abbreviated New Drug Applications (ANDAs)." (Plunkett Rep. at 4.) Two products are considered to be bioequivalent when they are equal in the rate and extent to which the active pharmaceutical ingredient (API) becomes available at the site(s) of drug action.[222] The bioequivalence standard does not address inactive ingredients or impurities.[223] Nor is there any regulatory provision that ties bioequivalence to adulteration. In any event, there cannot be any real dispute in this litigation as to whether the generic valsartan was bioequivalent to the RLD, because the FDA found as much in reviewing the ANDA and

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221 21 U.S.C. § 351.

222 *See* 21 C.F.R. § 320.1 (importing the definitions from 21 C.F.R. § 314.3); 21 C.F.R. § 314.3(b) (*Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.)

223 *See generally* 21 C.F.R. § 314.3(b) (*Bioequivalence*).

approving the generic product.[224] Bioequivalence reflects an FDA finding that was made before the products were ever sold to consumers, and Plaintiffs' experts cannot substitute the FDA's expert decision-making with their own.

212. Finally, Plaintiffs' experts are particularly off-base in their adulteration opinions because there is evidence that branded Diovan (the RLD) was contaminated with nitrosamines too. (*See, e.g.*, Plunkett Rep. at 4 ("Diovan . . . should not contain NDMA or NDEA."); Bain Rep. at 7 ("The approved forms of Diovan and Exforge did not include NDMA or NDEA impurities in any regulatory or compendial document describing the approved form of those drugs.").) In a June 2019 Citizen Petition, Valisure LLC and ValisureRX LLC reported a finding of NDMA in Novartis valsartan, which could only be a reference to branded Diovan because Novartis did not sell generic valsartan in the U.S.[225] Even if Plaintiffs' experts were correct in their misreading of the FDCA, it would make no sense to say that generic valsartan was adulterated because it had a contaminant that was not in the branded drug when there was a finding of NDMA in the branded drug as well.[226] Thus, not only are Plaintiffs' experts' opinions contrary to the FDCA and FDA regulations regarding adulteration, but they are also inherently illogical.

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224 ANDA 204821 for Valsartan Tablets USP, 40 mg, 80 mg, 160 mg and 320 mg was approved on 06/09/2015. *See* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204821.

225 *See* June 13, 2019 Valisure Citizen Petition.

226 *See id.*